Amikacin Liposome Inhalation Suspension (ALIS) for the Treatment of Nontuberculous Mycobacterial (NTM) Lung Disease Caused by *Mycobacterium avium* complex (MAC) in Adults

August 7, 2018

Insmed Incorporated

Antimicrobial Drugs Advisory Committee

Amikacin Liposome Inhalation Suspension (ALIS) Introduction

Paul Streck, MD

Chief Medical Officer

Insmed Incorporated

Proposed ALIS Indication

- For the treatment of Nontuberculous Mycobacterial (NTM) lung disease caused by *Mycobacterium avium* complex (MAC) as part of a combination antibiotic regimen in adults
  - Includes patients unresponsive to multidrug regimen treatment and newly diagnosed patients in certain circumstances
- Recommended ALIS dose is 590 mg QD

ALIS NDA Submitted Under Accelerated Approval Regulatory Pathway (Subpart H)

- Allows earlier approval of drugs based on surrogate endpoint
- Drugs must fulfill key criteria
  - Treat a serious condition (high mortality or morbidity)
  - Provide a meaningful advantage over available therapy
  - Demonstrate an effect on a surrogate endpoint reasonably likely to predict clinical benefit

ALIS Fulfills Criteria for Accelerated Approval

Criteria	Regulatory Fulfillment
A) Serious condition	✓ NTM lung disease caused by MAC is serious, with progressive morbidity and increased mortality risk
B) Meaningful advantage over available therapy	✓ No approved therapies for NTM lung disease caused by MAC ✓ Statistically significant attainment of culture conversion (3 consecutive monthly negative sputum cultures)
C) Demonstrated effect	✓ Culture conversion predicts durable culture conversion which then allows patients to stop NTM therapy

ALIS Granted Breakthrough Therapy, Qualified Infectious Disease Product and Orphan Designation

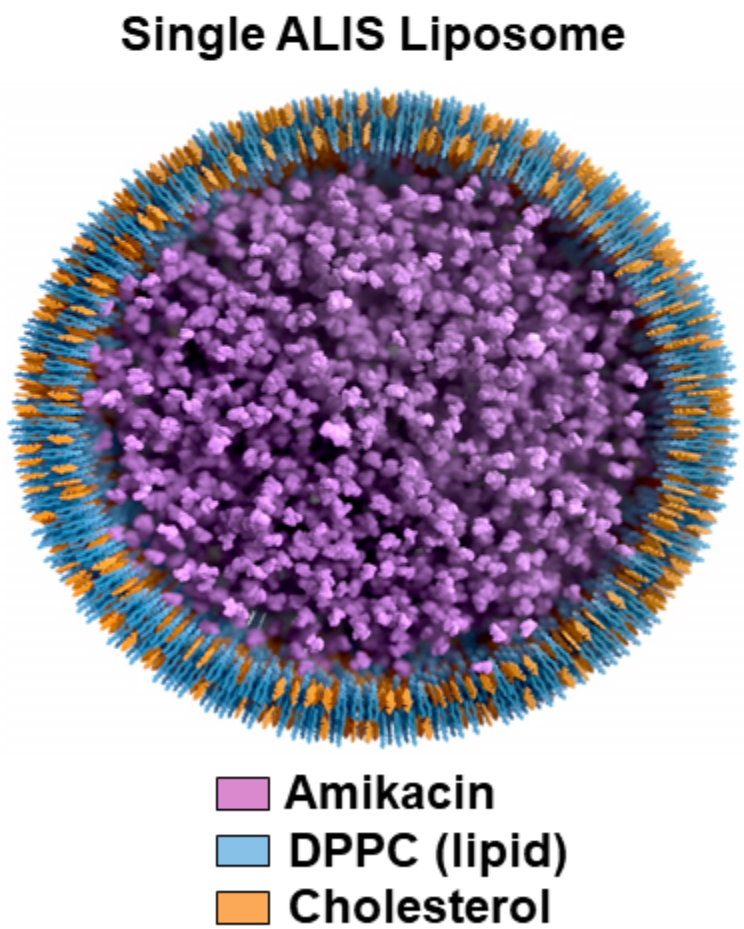
- Breakthrough designation for treatment of adult patients with NTM who are treatment refractory
  - Based on Study 112 results
- Qualified Infectious Disease Product designation
  - NTM organisms pose serious threat to public health
  - High unmet need for effective therapies
- Orphan designation

Amikacin for NTM Treatment

- Broad-spectrum aminoglycoside antibiotic
  - Disrupts and inhibits protein synthesis
- Amikacin shows activity against NTM
  - Parenteral administration
    - Poor lung tissue penetration
    - Known risk of systemic toxicity

Novel Inhaled Formulation of Amikacin

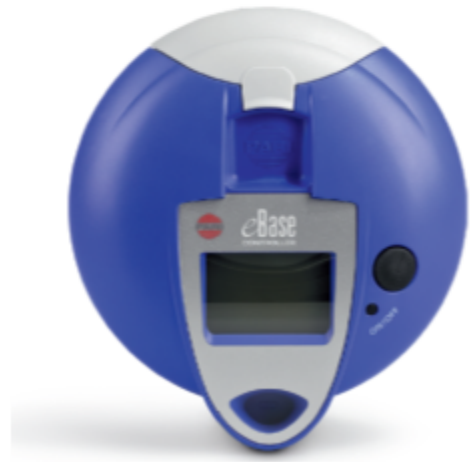
- ALIS composed of biocompatible lipids
- High drug to lipid ratio
- Liposomes suspended in 1.5% saline
  - Slightly hypertonic
  - Neutral pH (6.1 - 7.0)



ALIS Administered by Oral Inhalation to Enhance Lung Benefit, Minimize Systemic Risk

- Delivers liposomal amikacin directly to infection site
- Utilizes Lamira™ eFlow® Nebulizer System
  - Nebulizer handset and portable control unit approved and widely used for COPD and CF
- 70% aerosol droplets in respirable range (MMAD: 4.1 - 5.3 µm)

Handset



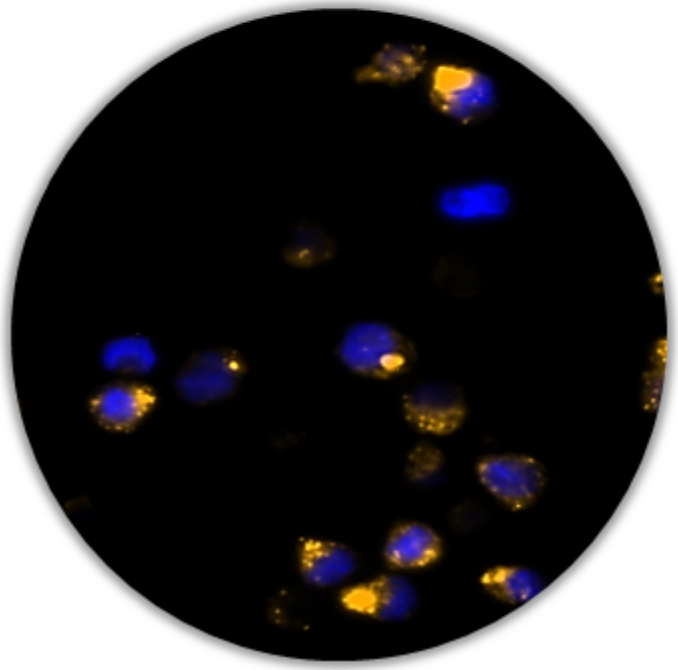
Portable Control Unit

MMAD = Mass Median Aerodynamic Diameter

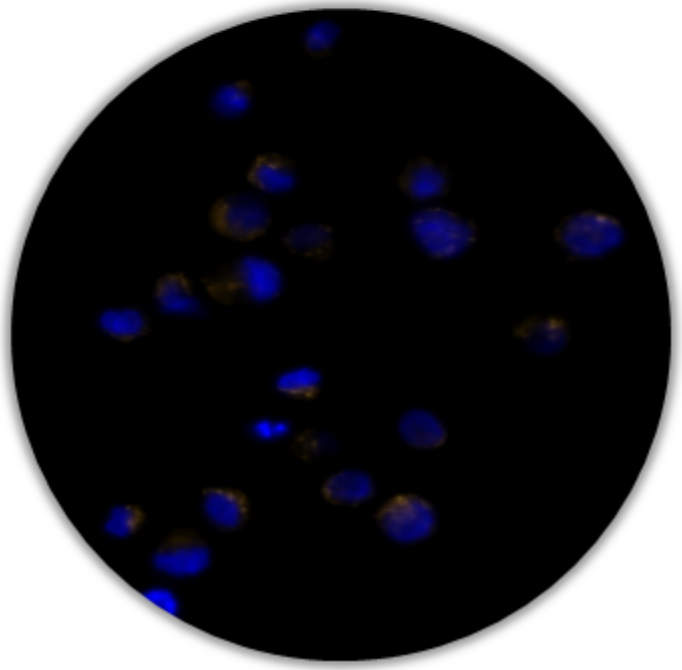
ALIS Has Unique Biological Attributes that Contribute to Efficacy Profile

- Liposome improves macrophage amikacin uptake
- 274-fold more amikacin into lung macrophages than IV amikacin
- Proven to penetrate MAC biofilms

ALIS



Free Amikacin



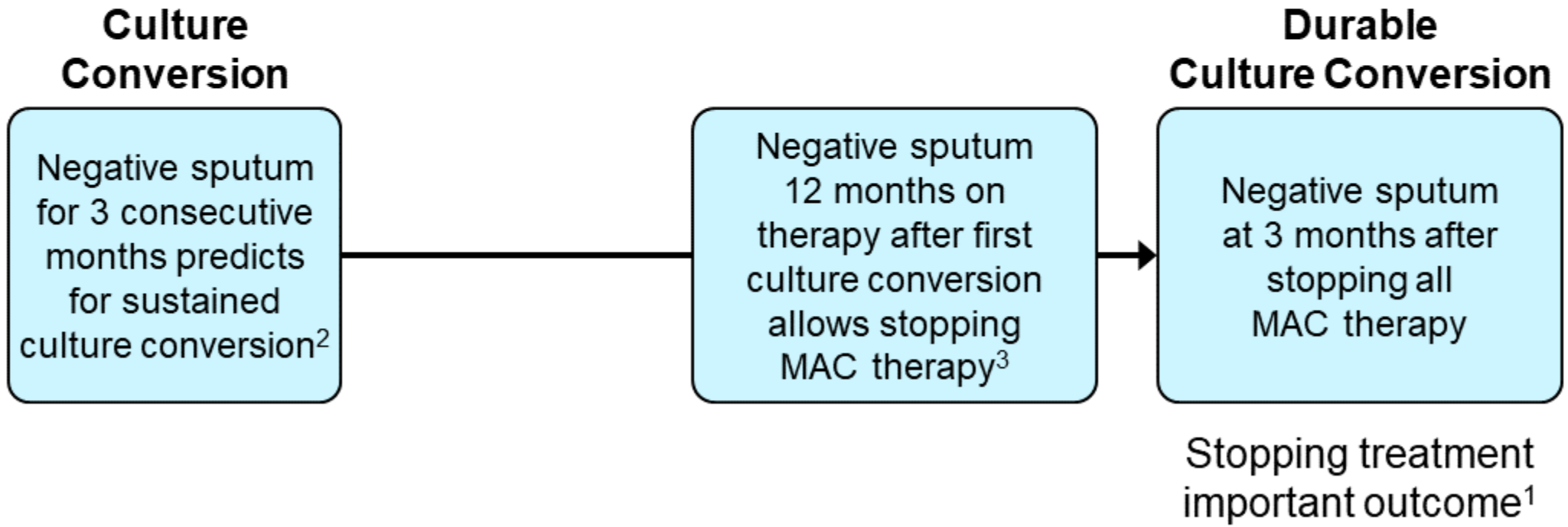
Labeled amikacin uptake into macrophage

Macrophage nuclei

Zhang et al., 2018

Goal of Treatment Is Durable Culture Conversion

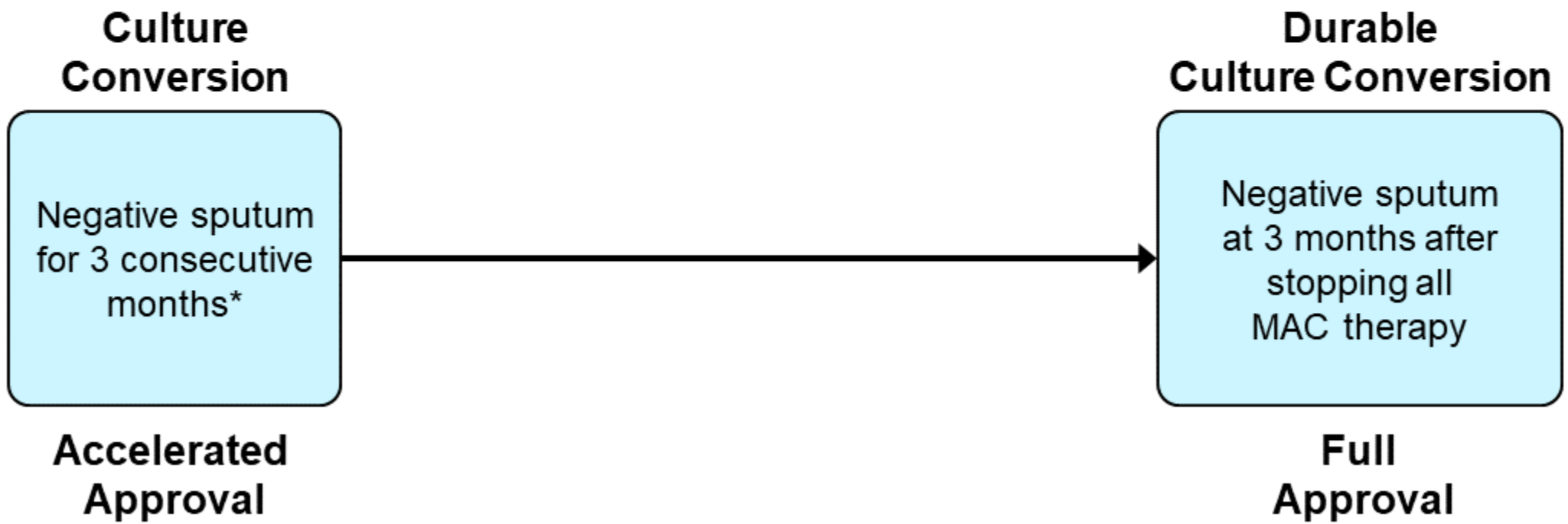
- Persistent negative samples indicate eradication of bacteria
- Expected to stop further lung damage and resulting morbidity



1) FDA's Patient-Focused Drug Development Workshop, 2015
2) Jeong et. al., 2015; Wallace et. al., 2014; Sim et. al., 2010; Fujikane et. al., 2005
3) Griffith et. al., 2007

Culture Conversion and Durable Culture Conversion Endpoints Support Accelerated and Full Approvals

- Prespecified endpoints in Study 212 and ongoing Study 212



*Multiple negative sputum samples on 3 consecutive months

ALIS NDA Supported by 3 Key Studies in Patients with NTM Unresponsive to Therapy for ≥ 6 Months

Supportive Phase 2	Pivotal Phase 3	Supportive Phase 3
Study 112 Randomized double-blind, placebo-controlled ALIS 590 mg QD + Multidrug Regimen vs Placebo + Multidrug Regimen	**Study 212** Randomized controlled open-label ALIS 590 mg QD + Multidrug Regimen vs Multidrug Regimen Alone	**Study 312** Open-label extension for Study 212 non-converters ALIS 590 mg QD + Multidrug Regimen

ALIS + Multidrug Regimen Provides Superior Culture Conversion by Month 6

- Culture conversion predicts durable culture conversion
  - Durable culture conversion allows patients to stop all MAC therapy
- Eradication of disease expected to improve morbidity
  - Patients who converted had greater improvement in 6MWT
- Inhalation minimizes systemic exposure and resultant toxicity associated with IV amikacin
- AEs primarily respiratory events
  - Most events mild to moderate

6MWT = 6-minute walk test

Agenda

Unmet Need	**Shannon Kasperbauer, MD** Associate Professor, Department of Medicine Division of Mycobacterial & Respiratory Infections National Jewish Health
Efficacy	**Eugene Sullivan, MD** Chief Product Strategy Officer Insmed Incorporated
Safety	**Peter Sallstig, MD** Vice President, Clinical Development Insmed Incorporated
Clinical Perspective	**David Griffith, MD** Professor of Medicine University of Texas Health Science Center at Tyler

Additional Experts

Pulmonologist / Chair of Data Monitoring Committee	**James Donohue, MD** Professor of Medicine, Pulmonary & Critical Care University of North Carolina at Chapel Hill
Pulmonologist	**Patrick Flume, MD** Powers-Huggins Endowed Chair Medical University of South Carolina
Statistics	**Mary Johnson, PhD** Statistical Consultant
Pharmacokinetics	**Christopher Rubino, PharmD** Executive Vice President Institute for Clinical Pharmacodynamics, Inc

Unmet Need

Shannon Kasperbauer, MD

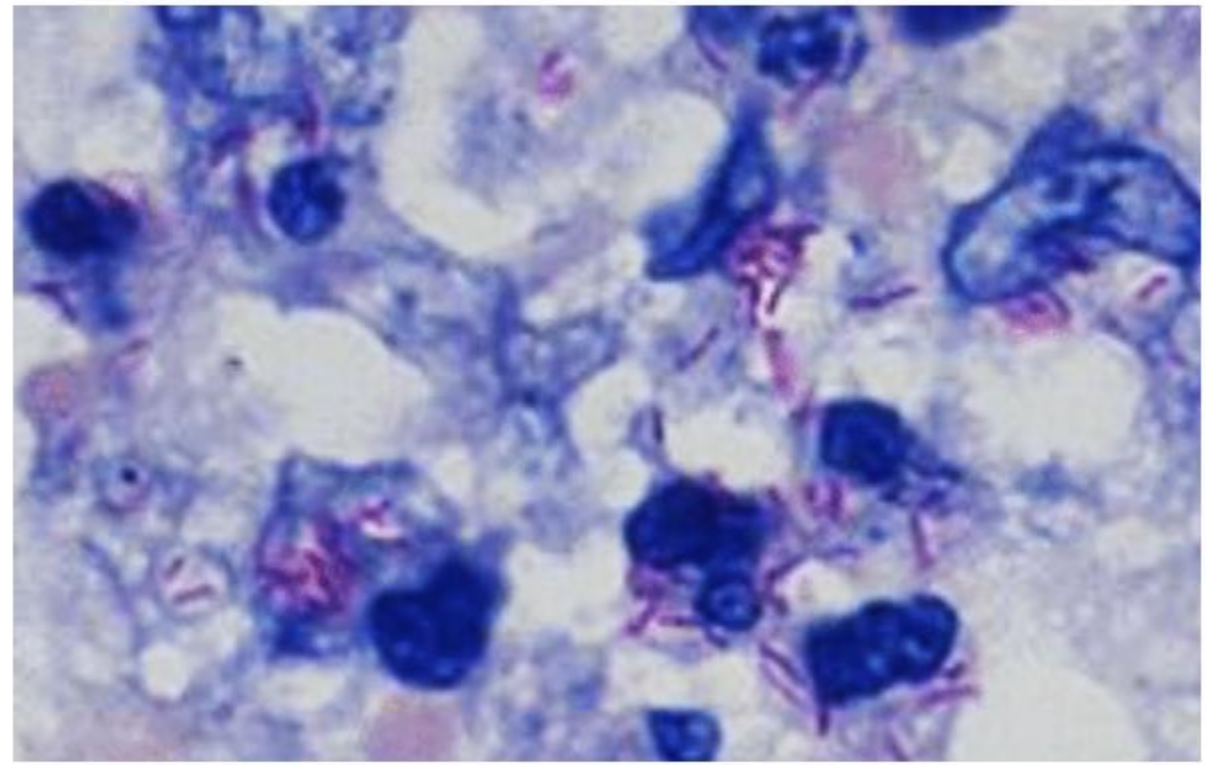
Associate Professor, Department of Medicine

Division of Mycobacterial & Respiratory Infections

National Jewish Health

Nontuberculous Mycobacteria (NTM)

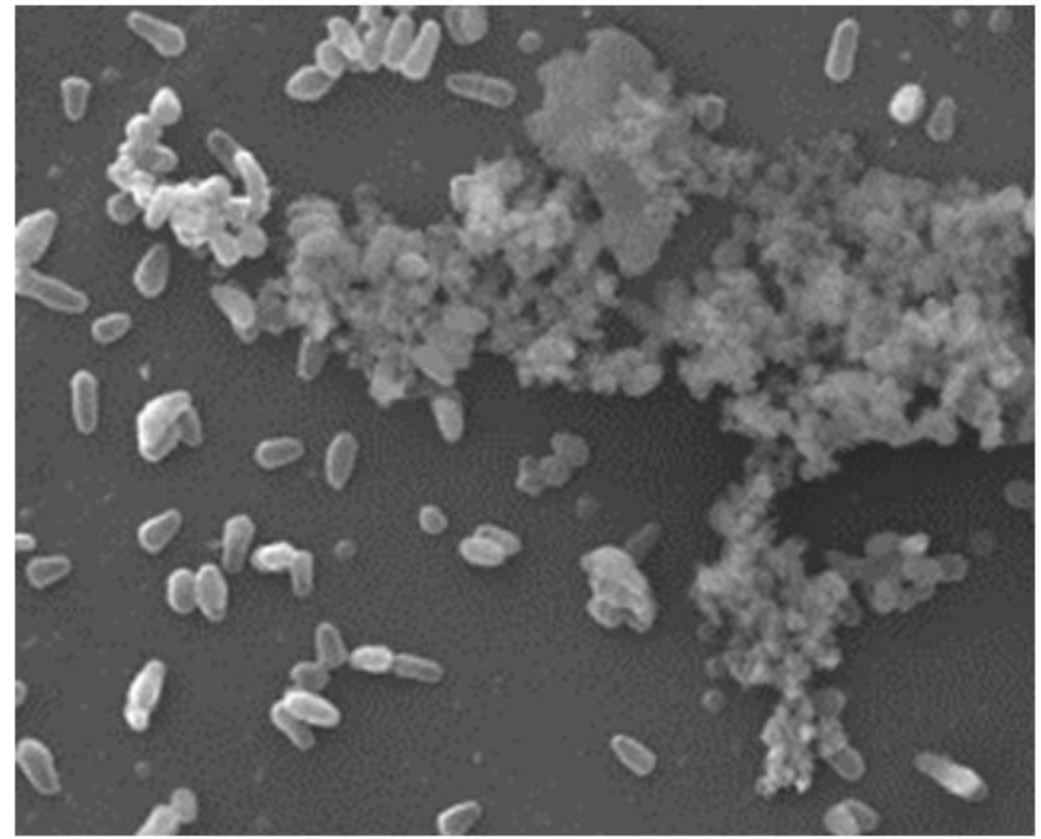
- Include nearly 200 mycobacterial species
- Ubiquitous in environment
- Transmitted via inhalation



AFB Staining (red)

NTM Causes Chronic, Indolent, and Progressive Lung Destruction

- Persist within lung tissue and pulmonary macrophages[1]
- Highly resistant to wide range of antibiotics[2]
  - Production of biofilms



Biofilm

1) Zhang et al., 2018
2) van Ingen et al., 2012

NTM Lung Disease Is Growing Concern

- > 80,000 people have NTM[1]
  - Annual prevalence increasing 8% per year[2]
- > 80% NTM lung disease caused by MAC[3]
- Serious and life-threatening disease

1) Strollo et al., 2015
2) Adjemian et al., 2012
3) Prevots et al., 2010

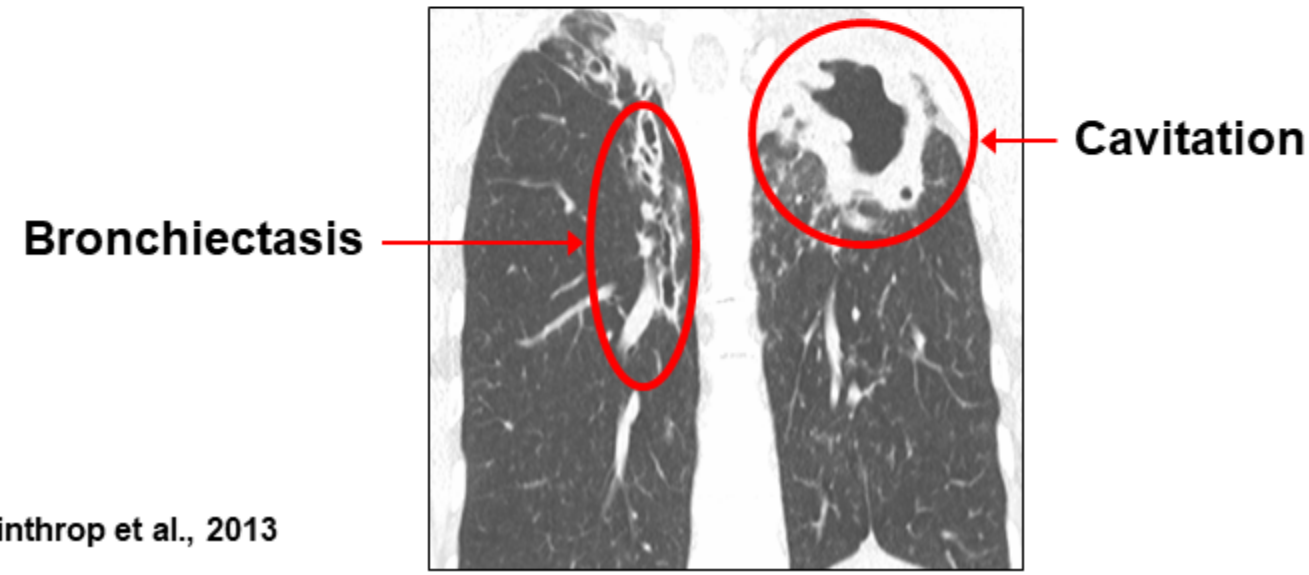
NTM Is Opportunistic Pathogen, Usually Occurring in People with Underlying Disease

Host Susceptibility Factors[1]

- Bronchiectasis or emphysema
- Genetic disorders that cause lung damage
- Immunodeficiencies

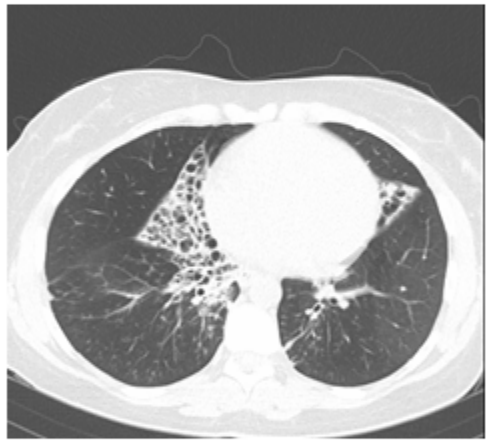
Prognostic Factors for Progression and Mortality[2]

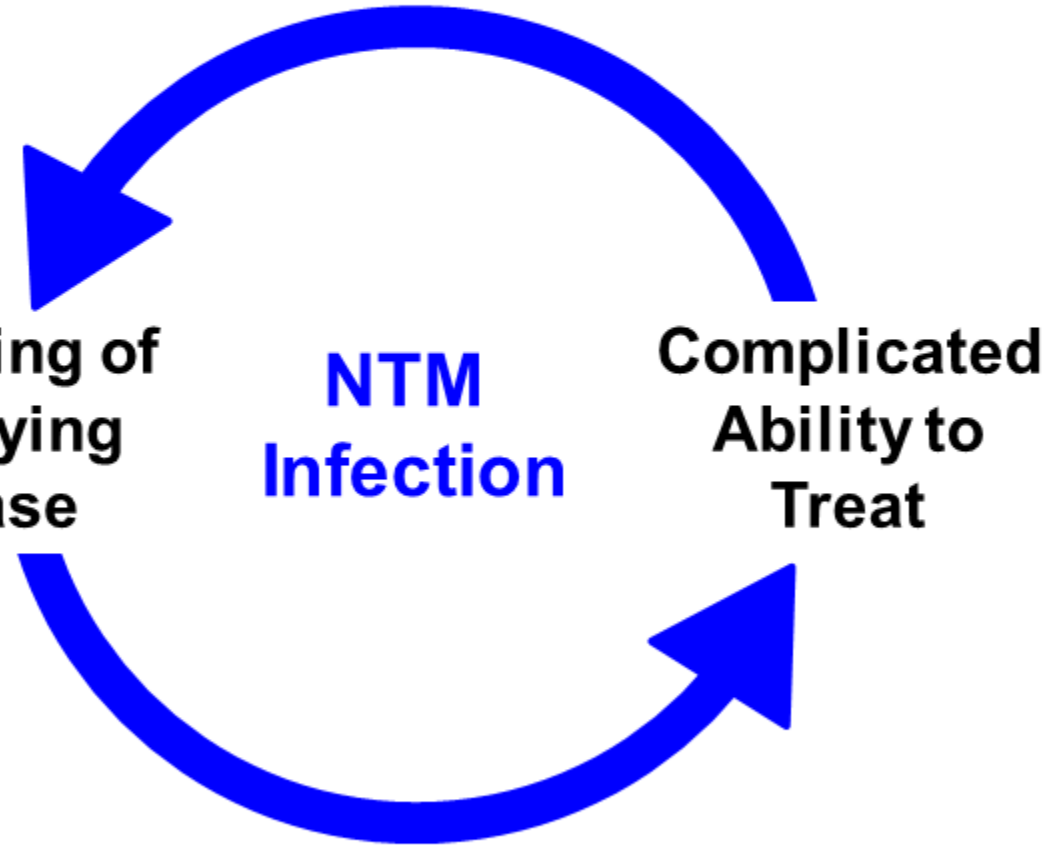
- Pulmonary hypertension
- Extensive disease
- Lung cavitation



1) Prevots et al., 2015; Brode et al., 2015; Adjemian et al., 2014; Winthrop et al., 2013
2) Kim et al., 2017; Lee et al., 2013; Hayashi et al., 2012

Structural Lung Damage Leads to Vicious Cycle that Impairs QoL



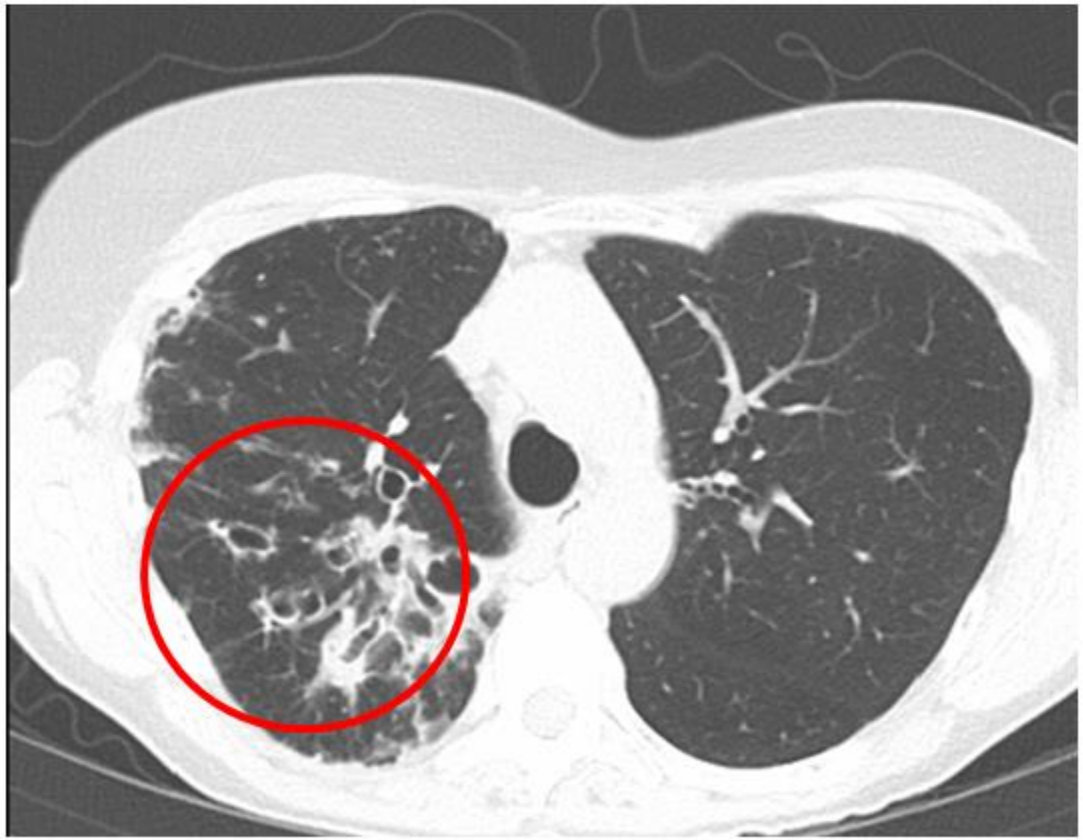


NTM Characterized by Symptoms that Worsen Over Time

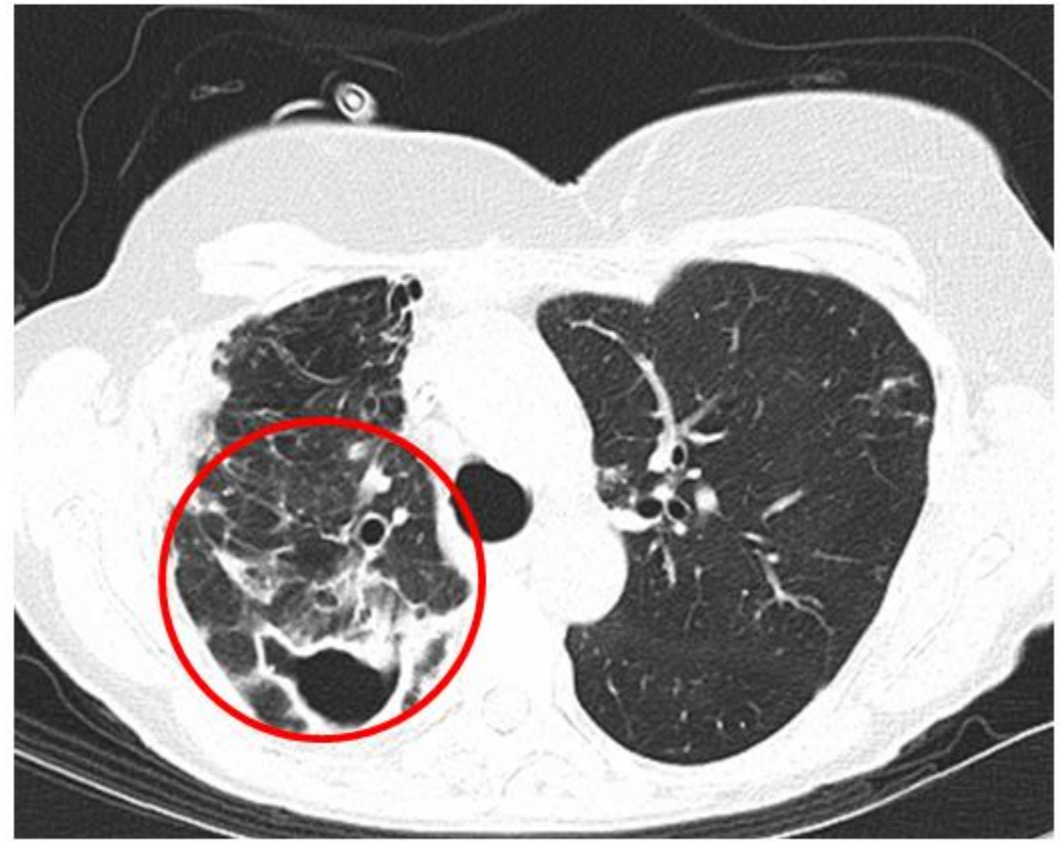
- Profound fatigue
- Loss of energy
- Malaise
- Chronic or recurring cough
  - Sputum production
- Fever
- Weight loss

Progressive Lung Damage in Patient with NTM Despite Treatment

2013



2017

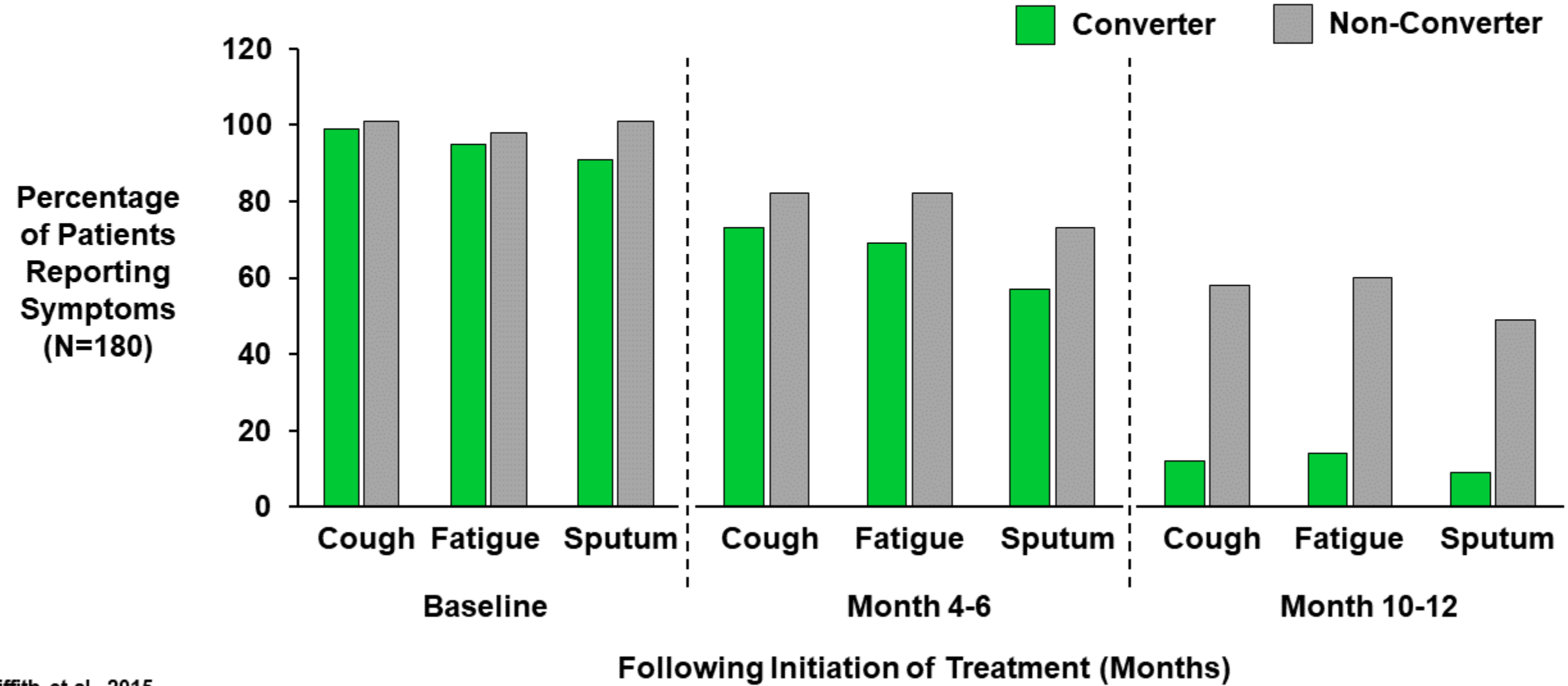


Goals of Therapy

- Durable culture conversion
- Radiographic improvement
- Symptomatic improvement

ATS/IDSA Statement; Griffith et al., 2007

Importance of Culture Conversion



Griffith et al., 2015

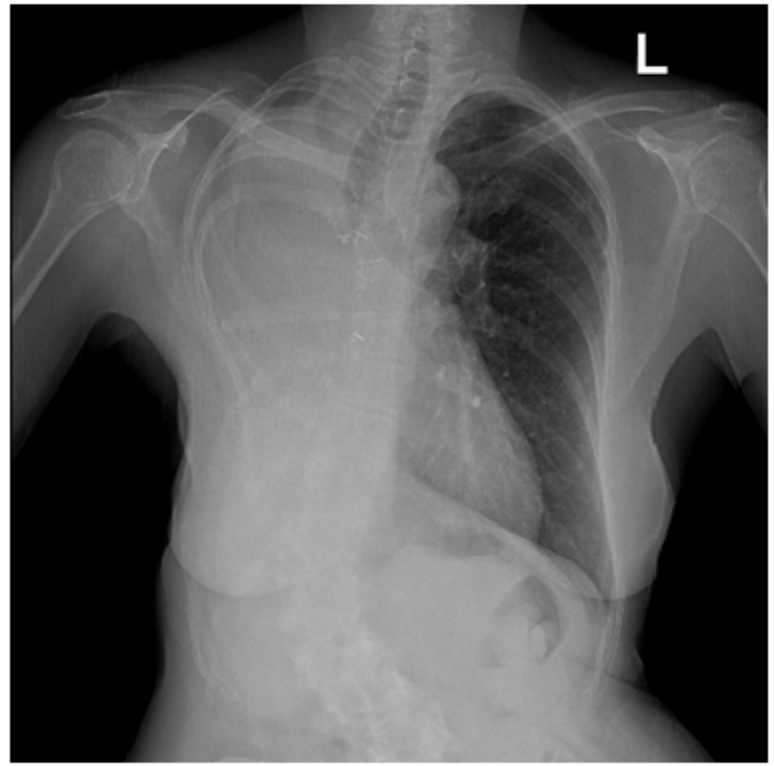
Standard of Care Treatment Is Lengthy and Challenging

- No FDA approved therapies
- Initial treatment = multiple drugs over prolonged therapy
  - 3 oral antibiotics ± parenteral aminoglycosides
  - Continued until culture conversion sustained for 12 months
- Successful therapy 12-18 months long
- Completing treatment difficult due to side effects and duration
- 40-60% achieve culture conversion on initial therapy
- Patients remain on therapy indefinitely in absence of culture conversion

ATS/IDSA Statement; Griffith et al., 2007

Limited Options for Patients Who Do Not Achieve Culture Conversion

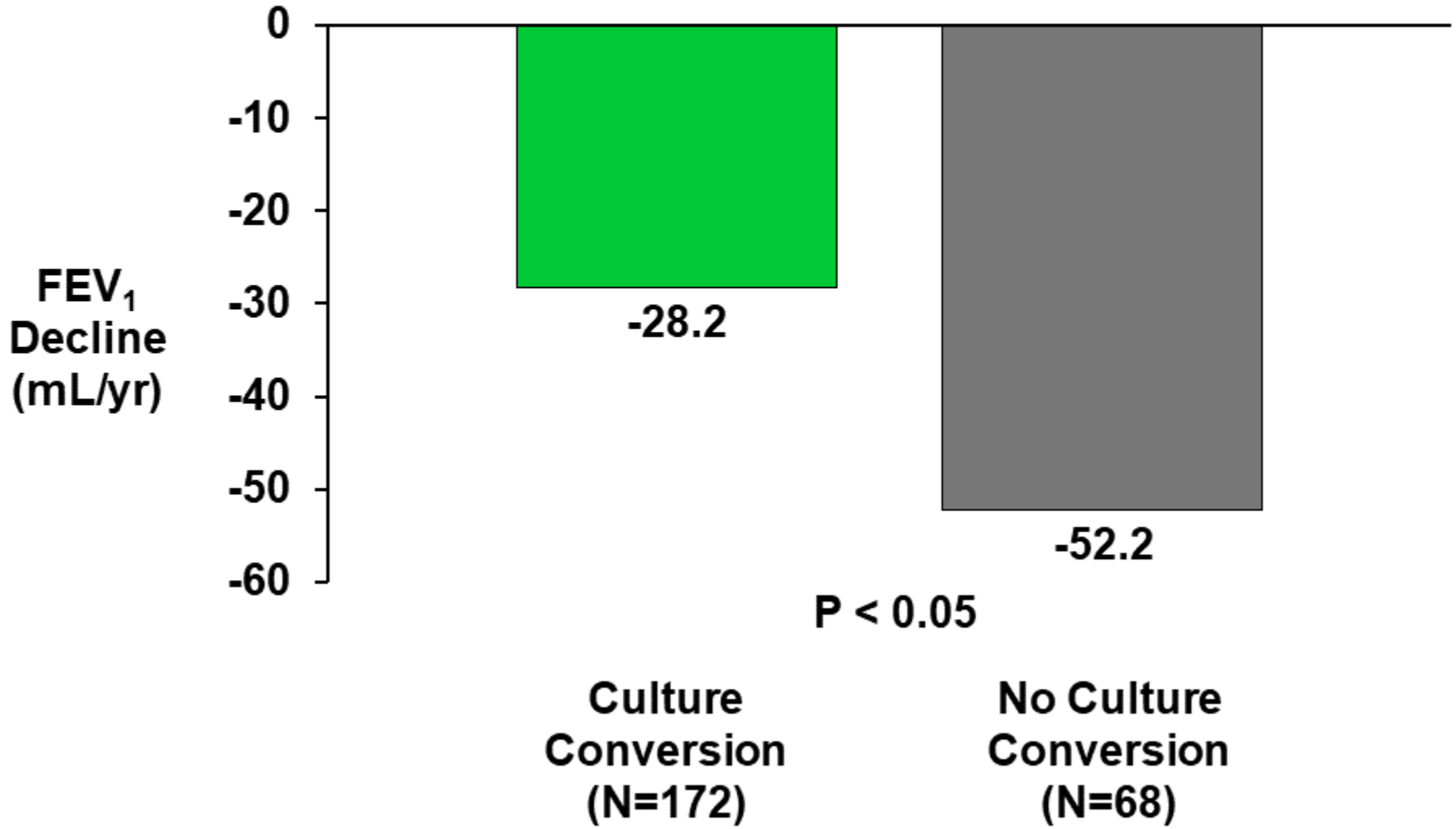
- Modification/intensification of first-line therapy[1]
- Addition of parenteral agent (e.g., amikacin)[1]
- Salvage therapies[1]
- Surgical resection[1]
- Treatment in refractory patients associated with poor efficacy[2]



Post-Pneumonectomy X-Ray

1) Griffith et al., 2012
2) Jo K-W et al., 2014

NTM Treatment Failure Associated with Lung Function Decline



Park H-Y et al., 2016

Morbidity and Mortality Rate Higher for Patients Not Achieving Culture Conversion

- All-cause 5-year mortality ranging from 5 - 40%[1]
- NTM-related deaths more frequent in patients with persistently positive cultures after 12 months of treatment[2]
- Increased risk of radiographic progression in patients persistently sputum positive[3]
- Untreated MAC lung disease showed radiographic deterioration in 98% within 6 years[4]

1) Hayashi et al., 2012; Andrejak et al., 2010
2) Jenkins et al., 2008
3) Pan et. al., 2017
4) Park et al., 2017

Unmet Need for Effective Evidence-Based NTM Treatment Option

- Offering chance for eradication of infection
- Potential to stop combination antibiotic therapy
- Could lead to improved morbidity and mortality outcomes
- Early treatment success may prevent progressive lung damage

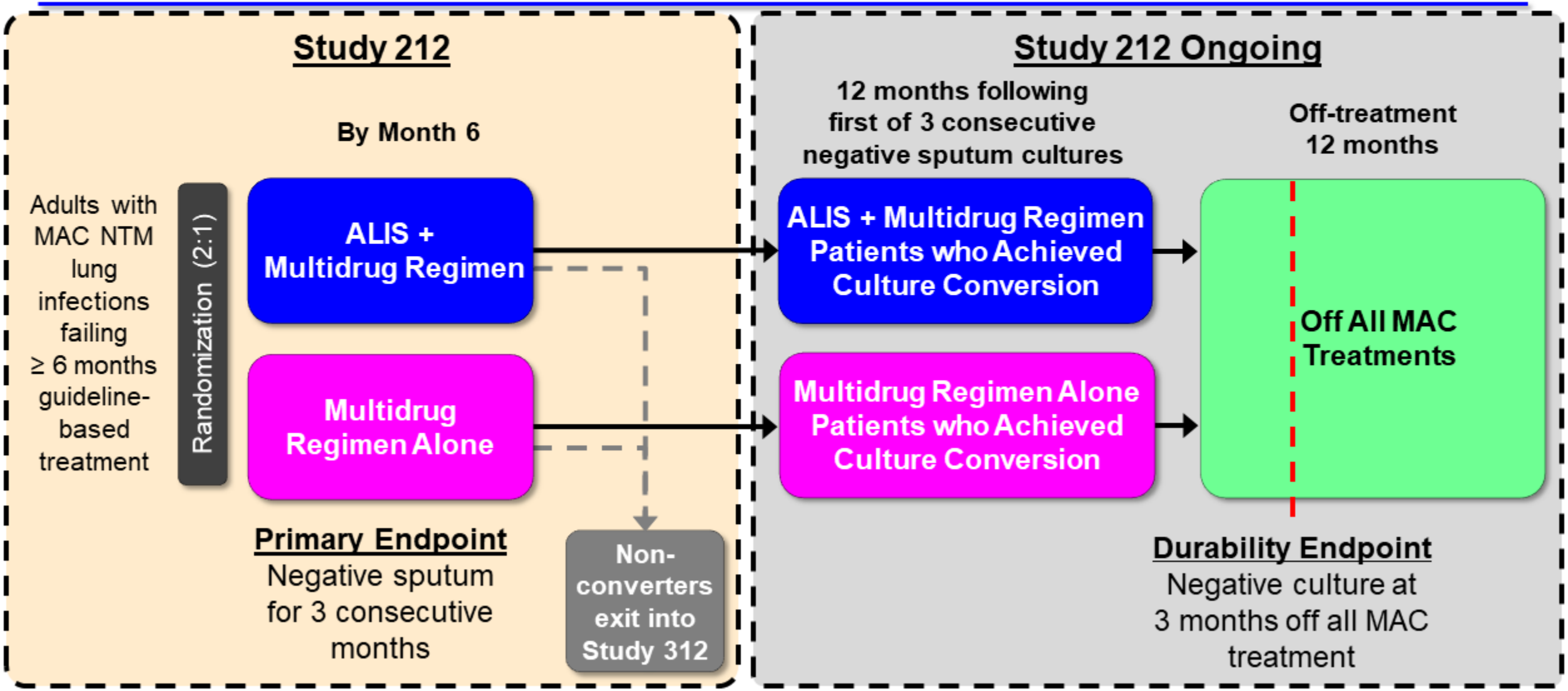
Efficacy

Eugene Sullivan, MD
Chief Product Strategy Officer
Insmed Incorporated

ALIS NDA Supported by 3 Key Studies in Patients with NTM

Supportive Phase 2	Pivotal Phase 3	Supportive Phase 3
Study 112 Randomized, double-blind, placebo-controlled ALIS 590 mg QD + Multidrug Regimen vs Placebo + Multidrug Regimen	**Study 212** Randomized controlled open-label ALIS 590 mg QD + Multidrug Regimen vs Multidrug Regimen Alone	**Study 312** Open-label extension for Study 212 non-converters ALIS 590 mg QD + Multidrug Regimen

Study 212: Randomized, Open-Label, Multicenter Study of ALIS + Multidrug Regimen



Study 212: Primary Endpoint Culture Conversion Is Goal of Antimicrobial Therapy

- Culture conversion
  - Multiple sputum samples obtained each month
  - Central labs blinded to treatment assignment
  - All samples negative for 3 consecutive months
  - Culture results blinded until Month 6 data available
  - Conversion date: Date of first of 3 consecutive monthly negative sputum cultures
- Culture conversion by Month 6 supports Accelerated Approval

Study 212: Secondary Endpoints Assess Clinical Impact of Culture Conversion at Month 6

- Secondary endpoints
  - Change in 6-minute walk test (6MWT) distance
  - Time to culture conversion
  - St. George's Respiratory Questionnaire (SGRQ)
- Exploratory endpoints
  - Change from baseline in 6MWT distance in converters vs non-converters, overall and by treatment arm

Ongoing Study 212 Will Confirm Durable Efficacy Once Patient Off All MAC Therapy for 3 Months

- Ongoing confirmatory study
  - Fully enrolled
- Converters complete additional 12 months of treatment following conversion date and stop all MAC therapy
- Durable efficacy based on negative cultures off all MAC therapy for 3 months
  - Confirmatory endpoint for full approval

Study 212: Enrolled Adult Patients Who Had Not Responded to Multidrug Regimen

- Persistently positive MAC cultures while on multidrug regimen, within 12 months of screening
  - ≥ 2 antibiotics
  - ≥ 6 consecutive months
- Positive for MAC with at least 2 positive sputum cultures
  - 1 positive culture within 6 months of screening
  - 1 positive culture at screening
- Susceptible amikacin MIC ≤ 64 µg/mL at screening

Study 212: Statistical Considerations

- 15% treatment effect in culture conversion by Month 6 determined to be meaningful
  - 20% rate of conversion for ALIS + Multidrug Regimen
  - 5% for Multidrug Regimen Alone
- N ~ 351 randomized (2:1 randomization), ITT analysis
  - Provide ≥ 90% power
  - 2-sided significance level of 0.05
- Dropouts prior to conversion considered treatment failures

Study 212: Balanced Baseline Demographics

	ALIS + Multidrug Regimen (N=224)	Multidrug Regimen Alone (N=112)
Mean age, years (SD)	65 (10)	65 (10)
Female	74%	61%
Region		
United States	42%	43%
Rest of the world	37%	39%
Japan	15%	13%
Asia (excluding Japan)	6%	5%
Ethnicity: Hispanic	5%	5%
Race		
White	71%	69%
Asian: Japanese	16%	13%
Asian: Other	10%	9%
Other	3%	9%

Study 212: Balanced Baseline Characteristics

	ALIS + Multidrug Regimen (N=224)	Multidrug Regimen Alone (N=112)
Number of drugs in regimen at screening		
0*	1%	3%
2	18%	13%
3	66%	75%
4+	15%	10%
Duration NTM lung disease, median (years)	4.5	3.3
Duration of Multidrug Regimen, (months)		
> 6 to ≤ 12	9%	10%
> 12 to ≤ 24	28%	30%
> 24	61%	58%

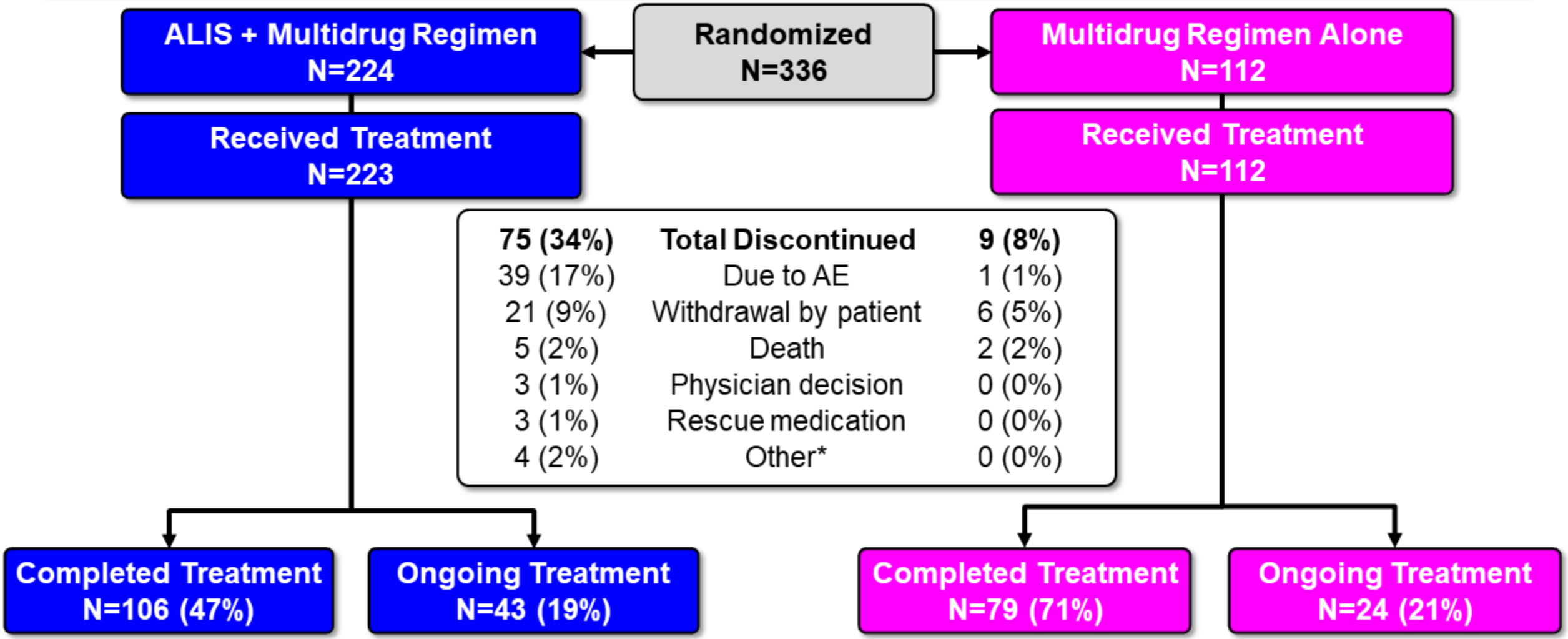
*4 subjects reinitiated their multidrug regimen after Day 7, and 1 subject withdrew consent at baseline

Study 212: Balanced Baseline Characteristics (cont'd)

	ALIS + Multidrug Regimen (N=224)	Multidrug Regimen Alone (N=112)
Underlying lung disease		
Bronchiectasis	65%	57%
COPD	13%	17%
COPD & bronchiectasis	10%	16%
Current smoker	12%	9%
Prior nebulized IV amikacin	11%	13%

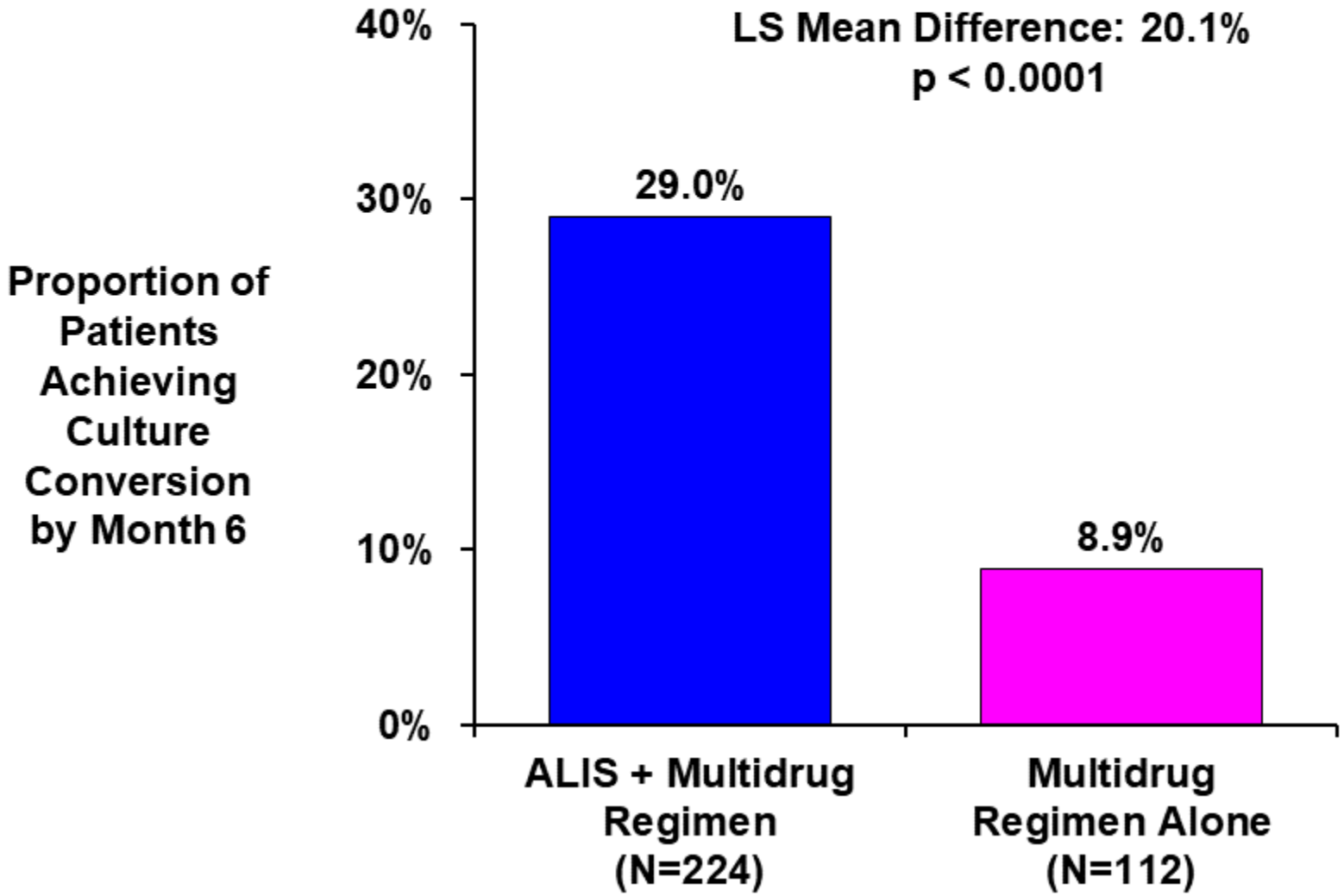
*4 subjects reinitiated their multidrug regimen after Day 7, and 1 subject withdrew consent at baseline

Study 212: Disposition at End of Treatment

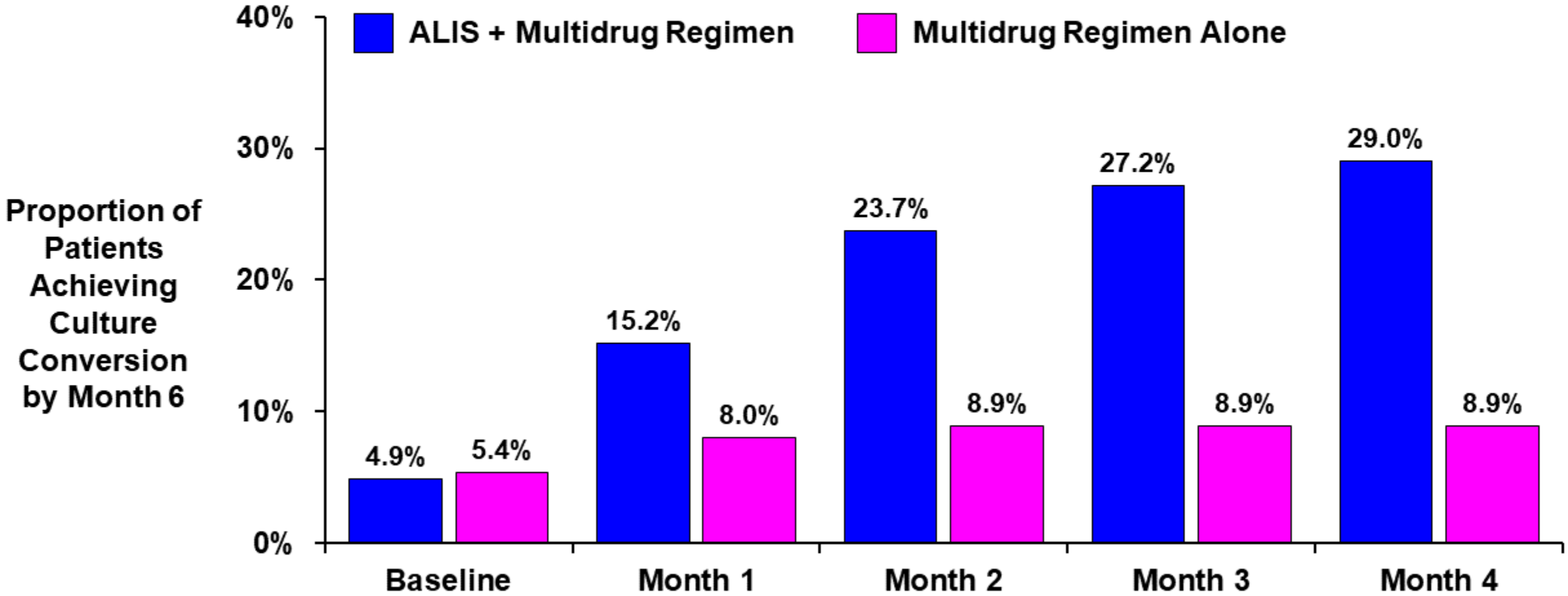


*Other includes categories: other, protocol deviation and non-compliance with study drug

Study 212: Primary Endpoint - Higher Proportion of ALIS Patients Achieved Culture Conversion

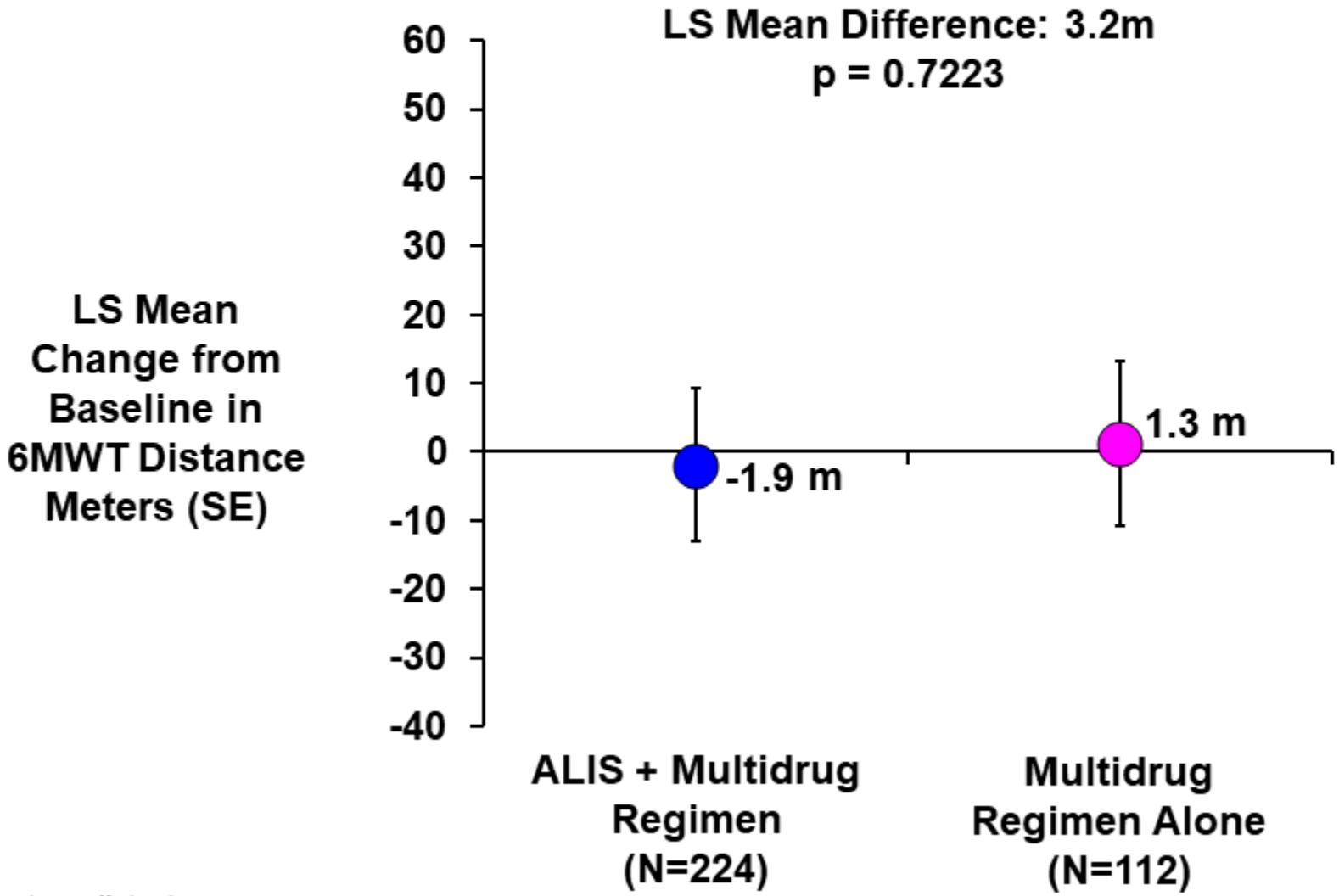


Study 212: Cumulative Proportion of Patients Achieving Culture Conversion



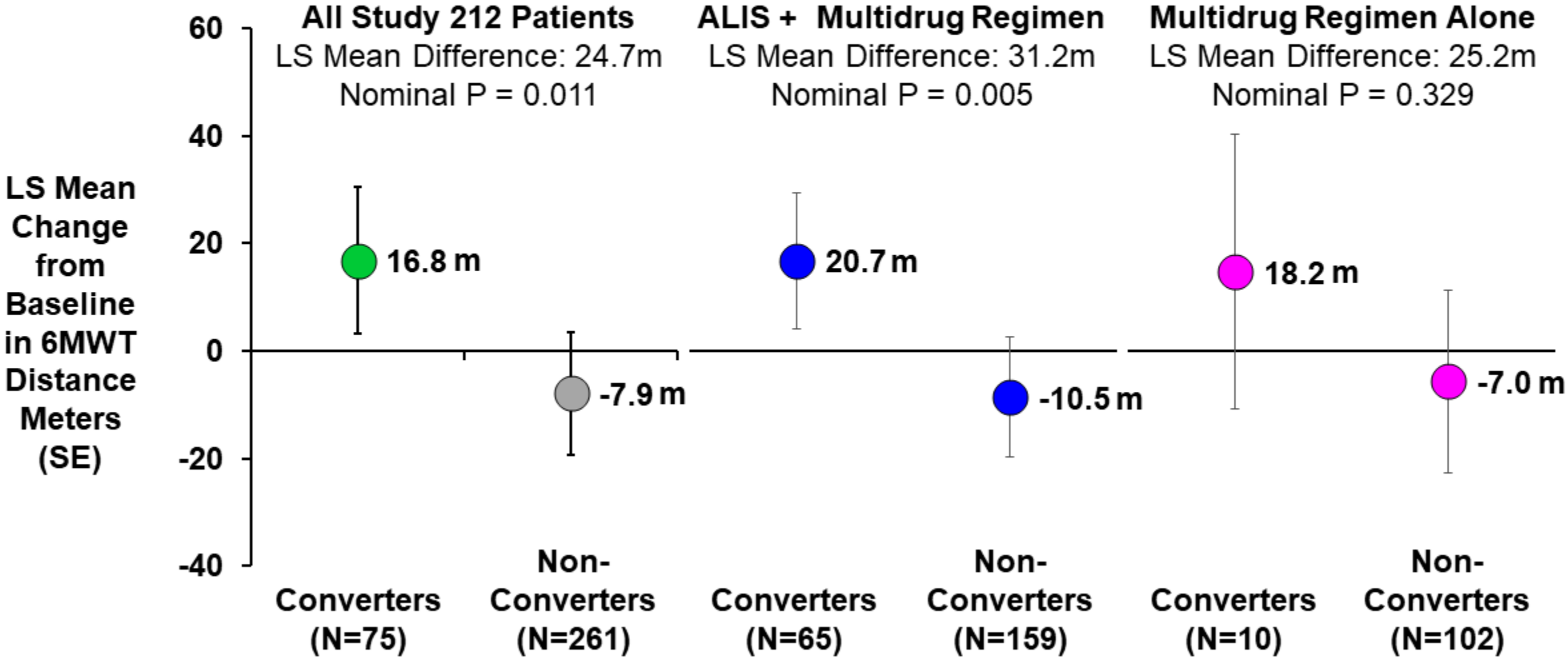
Culture conversion reported as first month of 3 consecutive monthly negative sputum samples

Study 212: Secondary Endpoint
Change from Baseline in 6MWT at Month 6

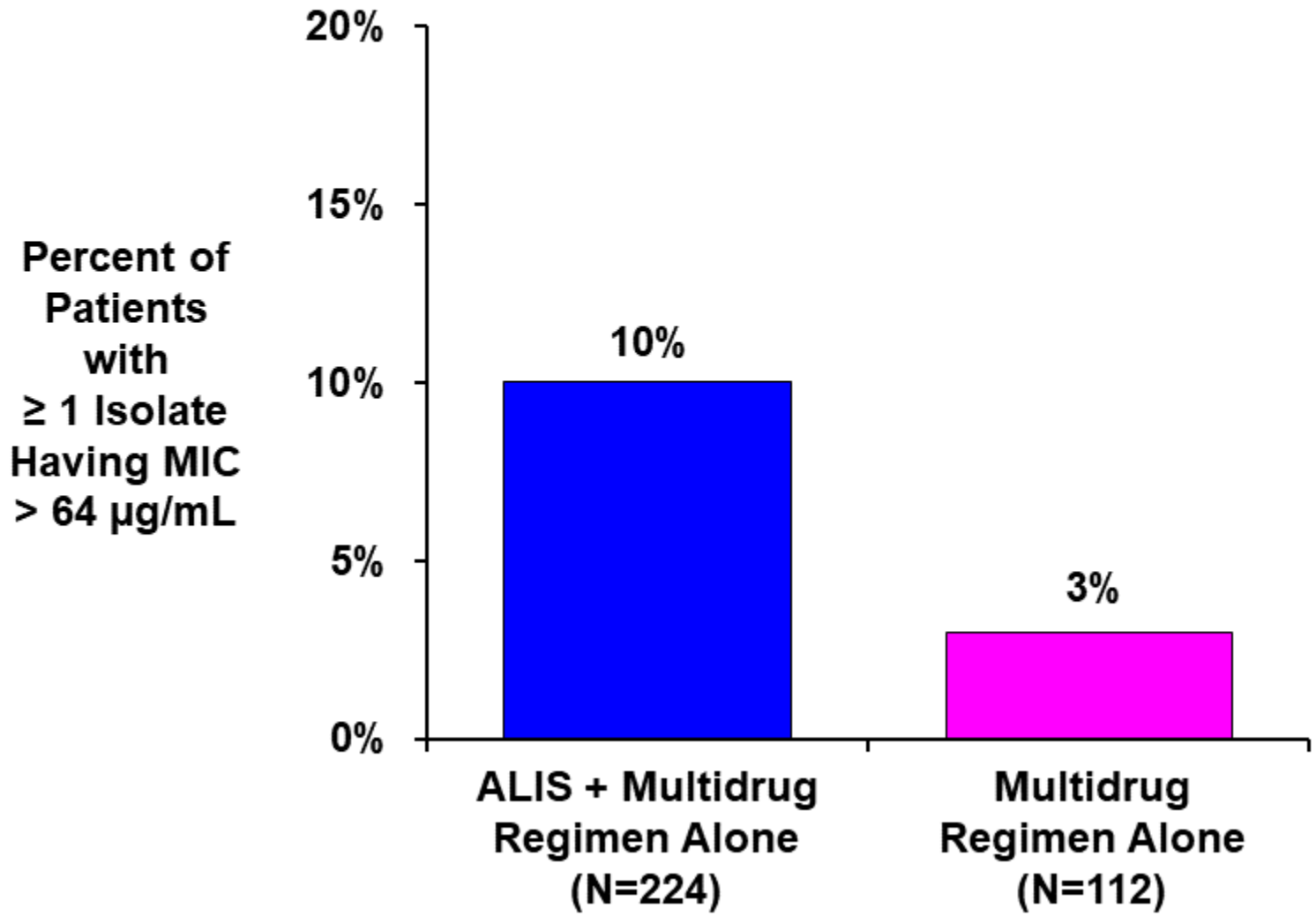


6MWT = 6-minute walk test

Study 212: Culture Conversion Associated with Improvement in 6MWT



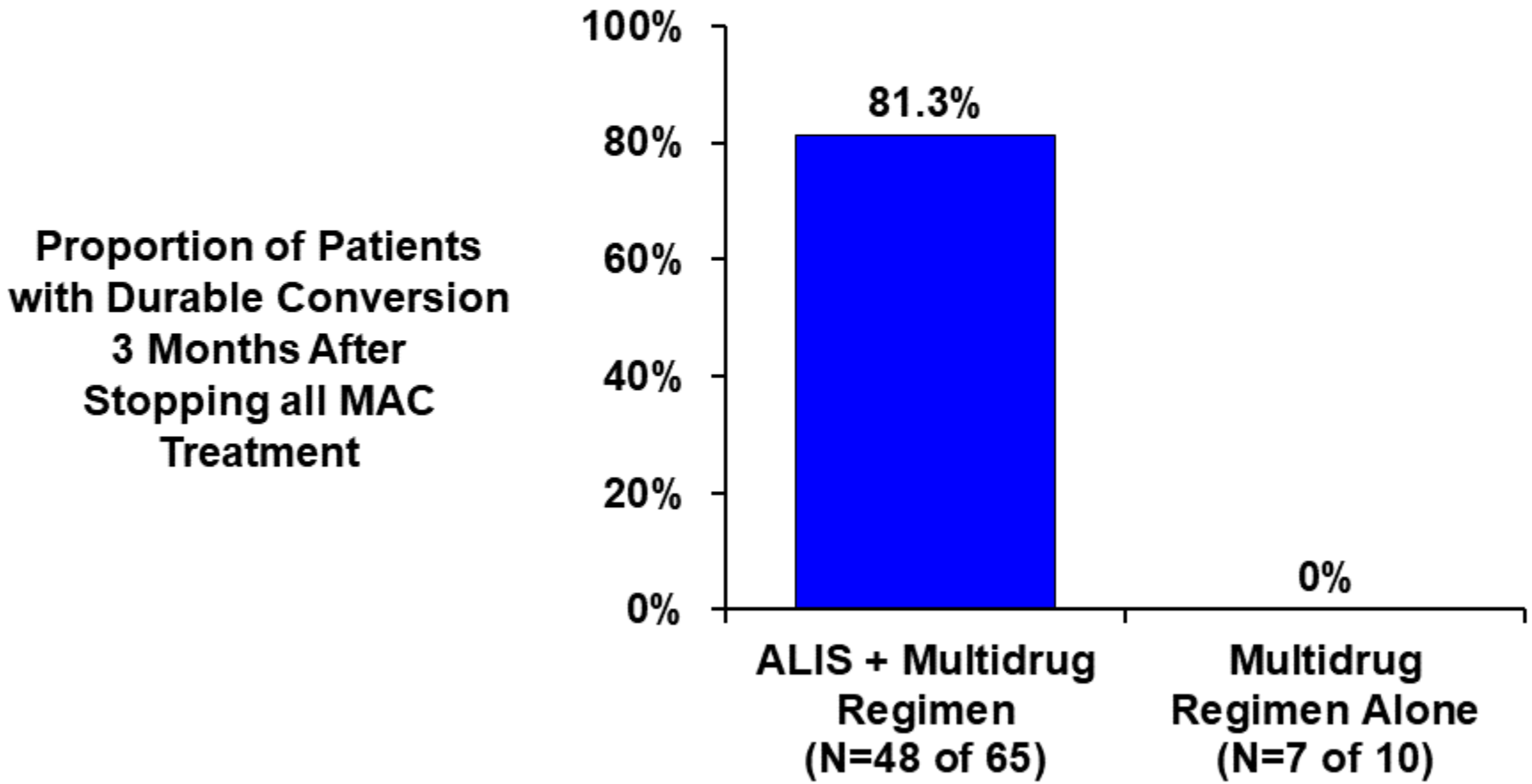
Study 212: Incidence of Post-Baseline MAC Isolates With MIC > 64 µg/mL Uncommon



Study 212 Supports that ALIS Improves Culture Conversion

- AMDAC asked to consider whether culture conversion by Month 6 is reasonably likely to predict clinical benefit
- Interim data from ongoing Study 212 provide encouraging evidence for durable culture conversion

Study 212 Interim Data: Month 6 Results Predict for Durable Culture Conversion



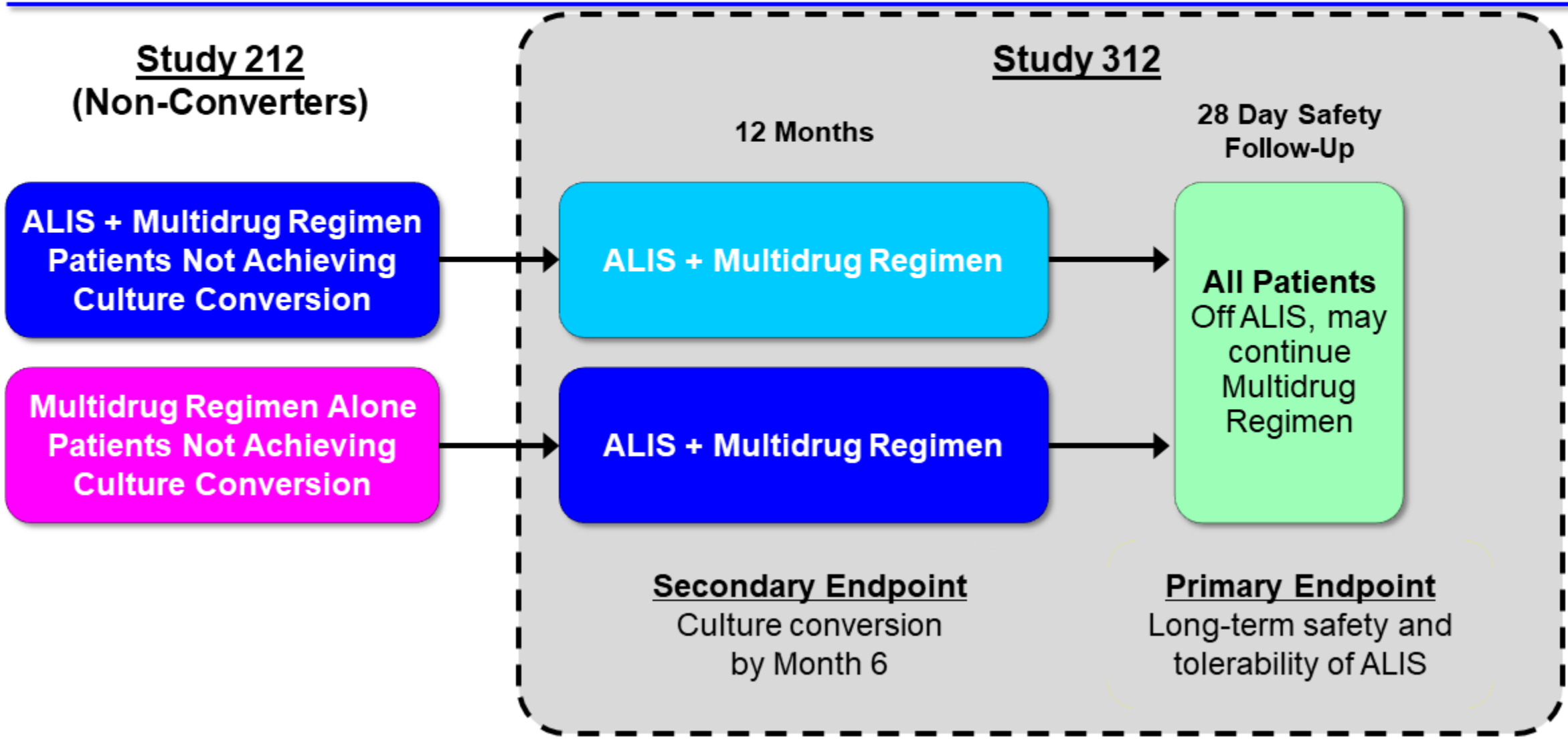
Data as of April 2018 in patients with samples

DATA HAS NOT YET BEEN REVIEWED BY THE FDA

ALIS NDA Supported by 3 Key Studies in Patients with NTM

Supportive Phase 2	Pivotal Phase 3	Supportive Phase 3
Study 112 Randomized double-blind, placebo-controlled ALIS 590 mg QD + Multidrug Regimen vs Placebo + Multidrug Regimen	**Study 212** Randomized controlled open-label ALIS 590 mg QD + Multidrug Regimen vs Multidrug Regimen Alone	**Study 312** Open-label extension for Study 212 non-converters ALIS 590 mg QD + Multidrug Regimen

Study 312: Open-Label Extension Study in Non-Converters from Study 212



Study 312: Efficacy Endpoint Selection to Support Results Observed in Pivotal Study 212

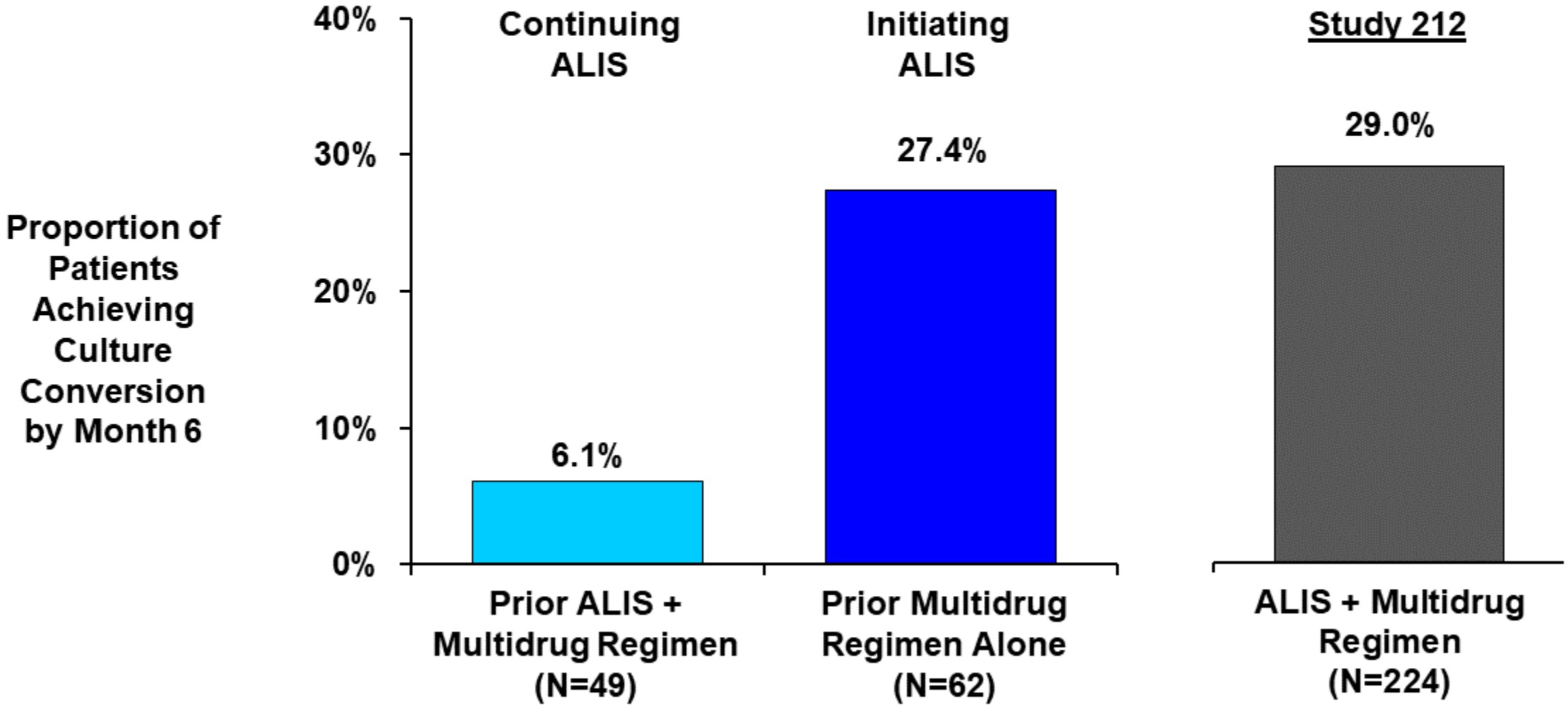
- Secondary endpoints
  - Culture conversion by Month 6
  - Time to culture conversion
  - Mean change from baseline in 6MWT at Month 6

Study 312: Culture Conversion Data Available at Time of Submission

	Prior ALIS + Multidrug Regimen (N=59)	Prior Multidrug Regimen Alone (N=74)
Patients Assessable for Culture Conversion*	49	62

*Patients with at least the first 3 monthly sputum culture results

Study 312: ALIS + Multidrug Regimen Achieved Culture Conversion in Refractory MAC Patients



Study 312: 8 of 133 Patients with ≥ 1 MAC Isolates Having MIC > 64 µg/mL

- 4 of 59 patients in Prior ALIS + Multidrug Regimen
- 4 of 74 patients in Prior Multidrug Regimen Alone

Study 112 (Ph 2): Supports that Culture Conversion Predicts for Durable Culture Conversion

Supportive Phase 2

Study 112

Randomized double-blind, placebo-controlled

ALIS 590 mg QD + Multidrug Regimen
vs
Placebo + Multidrug Regimen

Pivotal Phase 3

Study 212

Randomized controlled open-label

ALIS 590 mg QD + Multidrug Regimen
vs
Multidrug Regimen Alone

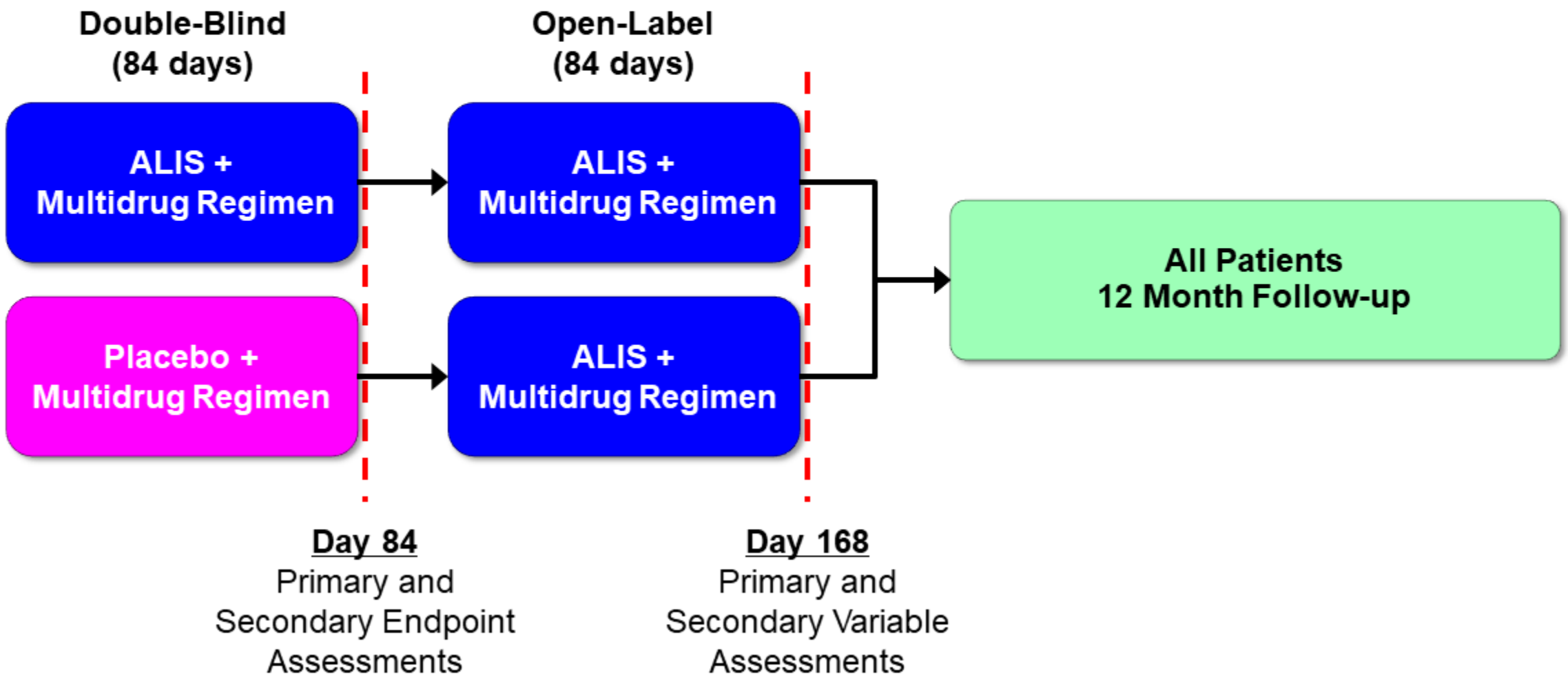
Supportive Phase 3

Study 312

Open-label extension for Study 212 non-converters

ALIS 590 mg QD + Multidrug Regimen

Study 112 (Ph 2): Randomized, Double-Blind, Placebo-Controlled Study in Refractory NTM Lung Disease



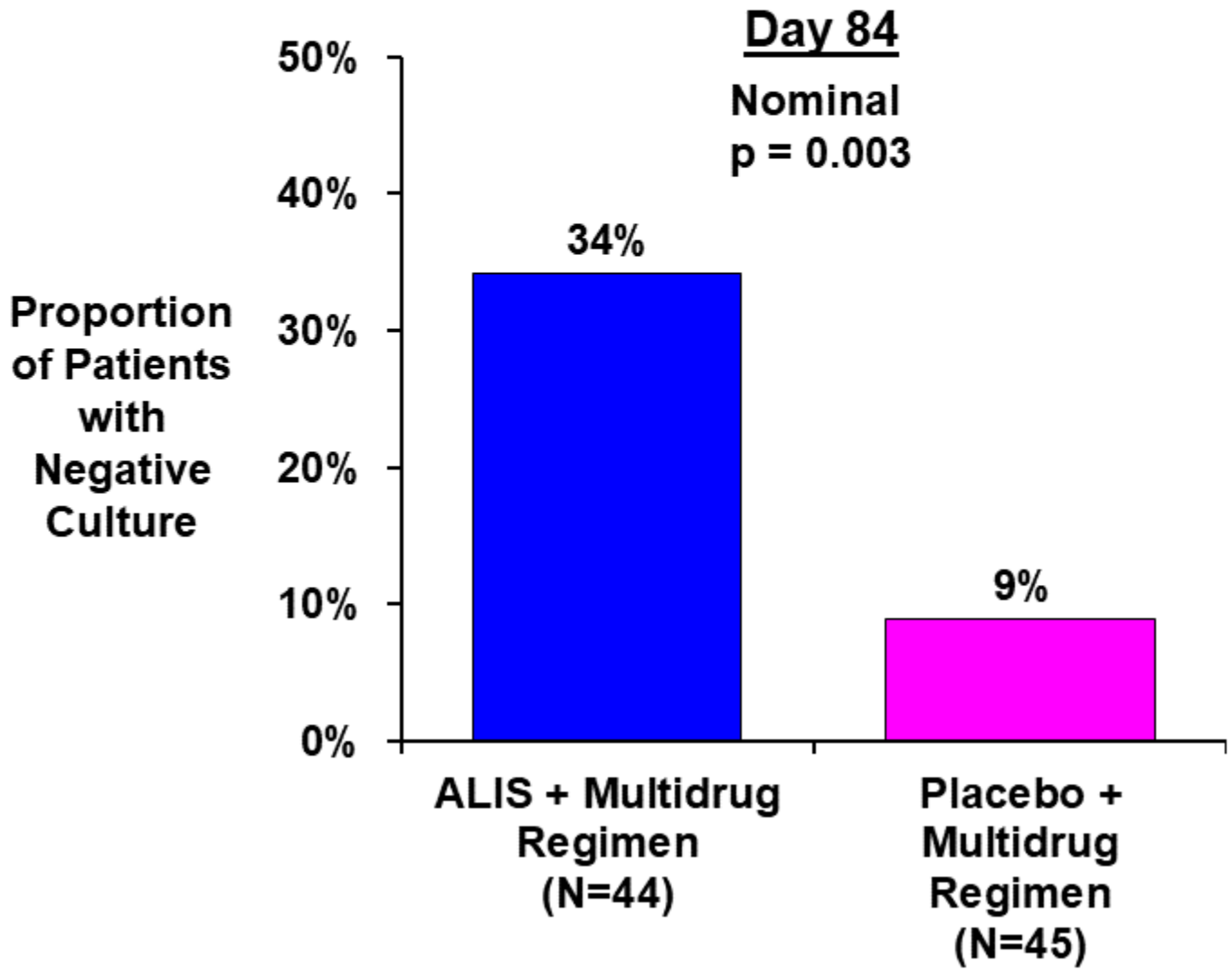
Study 112 (Ph 2): Prespecified Endpoints Intended to Assess Short-Term Efficacy Measures

- Primary endpoint
  - Mycobacterial density on semi-quantitative scale (SQS)
- Secondary endpoint
  - Proportion patients with negative sputum culture
- Post-hoc analysis
  - Culture conversion (3 consecutive negative cultures) assessed after open-label phase at Day 168
  - Durable culture conversion after 1 year off NTM therapy

Study 112 (Ph 2): Primary Endpoint Change from Baseline in SQS

- Trend in favor of ALIS + Multidrug Regimen did not reach statistical significance (p = 0.072)

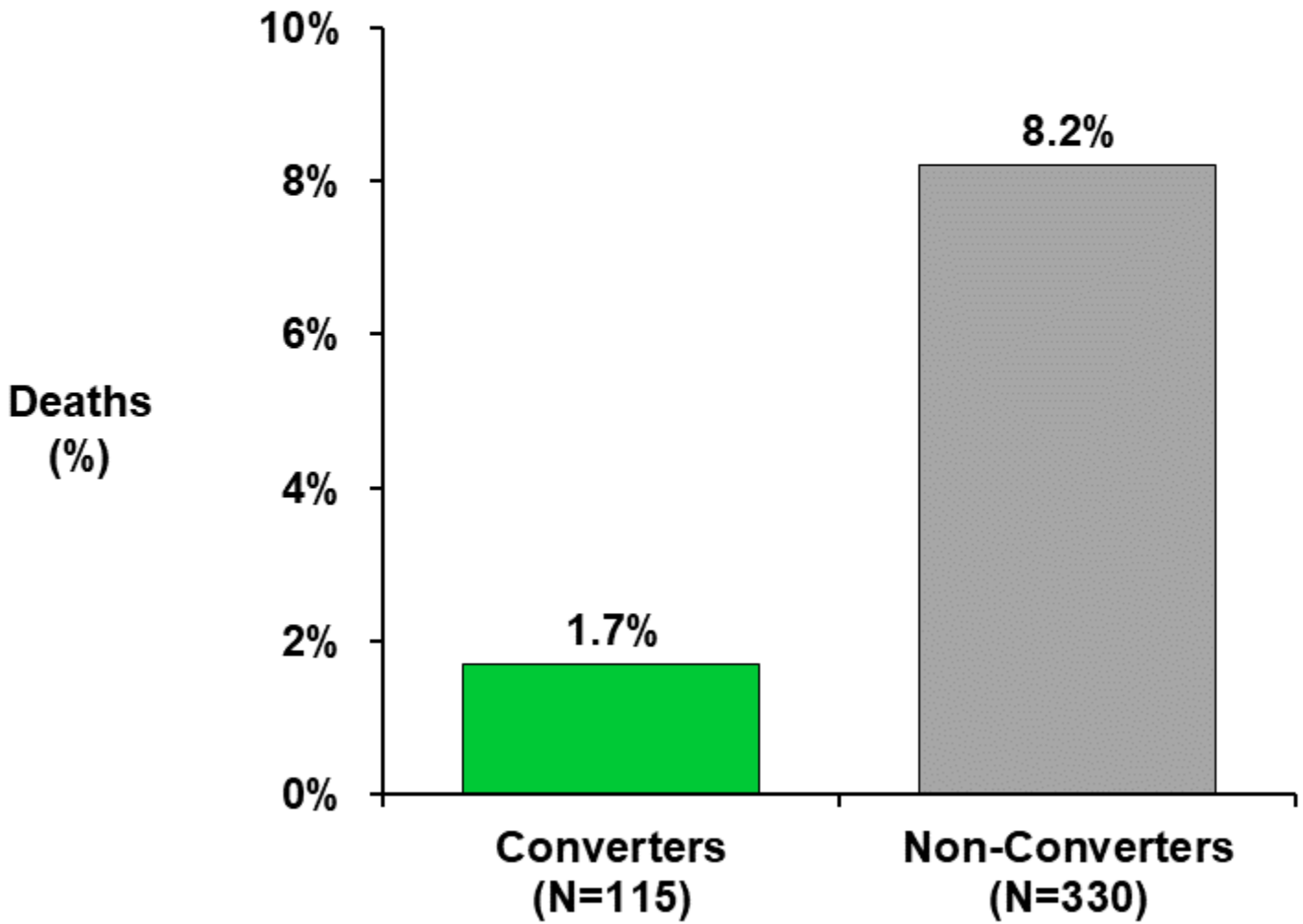
Study 112 (Ph 2): Secondary Endpoint Greater Proportion of Patients with Negative Culture at Day 84



Study 112 (Ph 2): Culture Conversion Predicted for Durable Culture Conversion

- 20 patients (22.5%) of patients achieved culture conversion
  - Defined as 3 consecutive monthly negative sputum cultures by Day 168
- 3 additional converters during 28-day off-treatment period
- 17 of 23 converters completed 12-month follow-up
  - 14 of 17 (82.4%) had sustained negative cultures 12 months after stopping ALIS

All NTM Studies: Culture Conversion May Be Associated with Decreased Mortality



Overall Efficacy Demonstrates Consistent Benefit of ALIS when Combined with Multidrug Regimen

- Study 212: Significantly greater proportion of ALIS patients achieved culture conversion by Month 6
  - Study 312: Refractory patients achieve culture conversion when adding ALIS to multidrug regimen
  - Study 112: Negative sputum culture and culture conversion data support efficacy shown in Study 212
- Study 112 and Study 212 interim durability data show culture conversion predicts for durable culture conversion
- Durable culture conversion allows patients to come off all MAC therapy
  - Expected to result in symptomatic and functional benefit

Safety

Peter Sallstig, MD

Vice President, Clinical Development

Insmed Incorporated

Overall Safety Data Support Favorable Benefit/Risk Profile

- Increase in AEs when ALIS added to multidrug regimen
- Most common AEs were respiratory events
  - Most were mild to moderate
  - Majority resolved without discontinuation
- SAEs and deaths similar between treatment arms

Populations Supporting Safety Profile of ALIS

Analysis Population	Study	ALIS + Multidrug Regimen	Multidrug Regimen
Primary	Study 212	223	112
NTM Pooled	Study 212	223	112
	Study 312	133[b]	-
	Study 112	91	45[a]
	Total patients	388[c]	157

a) Study 112 was blinded and patients treated with placebo
b) Study 312 includes patients from 212 Multidrug Alone (N=74) and ALIS non-converters (N=59)
c) Total number reflects unique patients who may have participated in multiple trials

Safety Exposure in NTM Studies

	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Mean exposure, days (SD)	214 (123)	232 (58)	199 (148)
Total patient years	105	56	164

Treatment-Emergent Adverse Event Definitions

Insmed Definition	FDA Definition
ALIS + Multidrug Regimen All AEs between Day 1 and within 28 days after last ALIS dose **Multidrug Regimen Alone** All AEs between Day 1 and within 28 days after the End of Treatment visit	All AEs between Day 1 and Day 247

Study 212: Safety Profile in Adults with NTM Caused by MAC

	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Any AE	98%	91%
Grade 1 - 2	79%	86%
Grade ≥ 3	21%	14%
SAEs	20%	18%
AE leading to death	3%	4%
AE leading to discontinuation of ALIS	18%	*NA*
AE leading to discont. of multidrug regimen	4%	3%

Study 212: Most Common AEs (ALIS + Multidrug Regimen, ≥ 10%)

Preferred Term	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Patients with ≥ 1 AE	98%	91%
Dysphonia	46%	1%
Cough	37%	15%
Dyspnea	22%	9%
Hemoptysis	18%	13%
Fatigue	16%	7%
Diarrhea	13%	5%
Nausea	11%	4%
Oropharyngeal pain	11%	2%
Headache	10%	5%

Study 212: Severity and Course of Most Common Respiratory AEs (ALIS + Multidrug Regimen ≥ 10%)

	Dysphonia (n=223)	Cough (n=223)	Dyspnea (n=223)	Hemoptysis (n=223)	Oropharyngeal Pain (n=223)
Patients with ≥ 1 AE	46%	37%	22%	18%	11%
Grade ≥ 3	2%	< 1%	3%	3%	0
Interruption of ALIS	15%	8%	9%	4%	2%
Resolved	13%	7%	7%	4%	2%
Discontinuation of ALIS	2%	1%	3%	1%	0%
Resolved	2%	1%	2%	1%	0%

Study 212: Incidence of Grade ≥ 3 AEs Higher in ALIS Patients (≥ 1%)

Preferred Term	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Patients with ≥ 1 Grade ≥ 3 AE	21%	13%
COPD	3%	0%
Dyspnea	3%	0%
Hemoptysis	3%	3%
Dysphonia	2%	0%
Pneumonia	2%	2%
Infective exacerbation of bronchiectasis	1%	2%
Alveolitis allergic	1%	0%
Pneumothorax	1%	1%
Respiratory failure	1%	1%
Aphonia	1%	0%

Study 212: Severity and Course of Grade ≥ 3 AEs Higher in ALIS Patients

	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Patients with ≥ 1 Grade ≥ 3 AEs	21%	13%
Interruption of ALIS	9%	*NA*
Resolved	8%	*NA*
Discontinuation of ALIS	5%	*NA*
Resolved	4%	*NA*

Study 212: AEs Leading to Discontinuation of ALIS (ALIS + Multidrug Regimen > 0.5%)

Preferred Term	ALIS + Multidrug Regimen (N=223)
Patients with ≥ 1 AE leading to discontinuation	18%
Dyspnea	3%
Dysphonia	2%
Hypoacusis	< 1%
Infective exacerbation of bronchiectasis	< 1%
Alveolitis allergic	< 1%
COPD	< 1%
Cough	< 1%
Hemoptysis	< 1%

Study 212: Incidence of SAEs Between Treatment Arms (ALIS + Multidrug Regimen ≥ 1%)

Preferred Term	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Patients with ≥ 1 SAE	20%	18%
Pneumonia	4%	2%
COPD	3%	1%
Infective exacerbation of bronchiectasis	2%	3%
Hemoptysis	3%	5%
Dyspnea	1%	0
Pneumothorax	1%	1%

Study 212: Severity and Course of SAEs

	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Patients with ≥ 1 SAE	20%	18%
Interruption of ALIS	9%	*NA*
Resolved	7%	*NA*
Discontinuation of ALIS	5%	*NA*
Resolved	4%	*NA*

Study 212: Incidence of Hospitalizations

	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)
Patients hospitalized	42 (19%)	15 (13%)
# of Unique Hospitalizations	79	25

Day 1 to Day 247

Study 212: Adverse Events Leading to > 2 Hospitalizations

Preferred Term, n (%)	ALIS + Multidrug Regimen	Multidrug Regimen Alone
# of Unique Hospitalizations	79	25
Exacerbation of COPD	15 (19%)	2 (8%)
Pneumonia	15 (19%)	3 (12%)
Hemoptysis	7 (9%)	5 (19%)
Infective exacerbation of bronchiectasis	6 (8%)	3 (12%)
Respiratory failure	5 (6%)	2 (8%)
Pneumothorax	4 (5%)	1 (4%)

NTM Pooled Population: Similar Proportion of Fatal AEs

Respiratory AESIs Category	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Any AE leading to death, n (%)	6 (3%)	5 (4%)	9 (2%)
Respiratory failure	2	1	2
COPD	1	0	2
Pneumonia	0	1	1
Acute respiratory distress syndrome	0	0	1
Lower respiratory tract infection	0	0	1
Lung infection	1	0	1
Pulmonary embolism	1	0	1
Cachexia	1	0	1
MAC infection	0	1	0
Cardiogenic shock	0	1	0
Interstitial lung disease	0	1	0

Adverse Events of Special Interest (AESI)

- Respiratory AEs
- Known systemic AE risks with IV amikacin

Respiratory AESIs

Respiratory AESIs	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Bronchospasm AESIs	29%	12%	25%
Hemoptysis AESIs	17%	13%	17%
COPD exacerbation AESIs	8%	4%	6%
Allergic alveolitis AESIs	3%	1%	3%

Bronchospasm

Respiratory AESIs Preferred Terms	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Bronchospasm AESIs	29%	12%	25%
Dyspnea	22%	9%	17%
Wheezing	7%	3%	6%
Bronchospasm	3%	0%	3%
Asthma	1%	0%	1%
Bronchial hyperreactivity	< 1%	0%	< 1%
Dyspnea exertional	< 1%	0%	< 1%
Throat tightness	< 1%	0%	< 1%

Exacerbation of COPD

Respiratory AESIs Preferred Terms	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Exacerbation of COPD AESI	8%	4%	6%
Infective exacerbation of COPD	1%	1%	< 1%
COPD	8%	3%	6%

Allergic Alveolitis

Respiratory AESIs Preferred Terms	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Allergic alveolitis AESIs	3%	1%	3%
Pneumonitis	2%	0%	2%
Alveolitis allergic	1%	0%	1%
Interstitial lung disease	< 1%	1%	1%
Respiratory disorder	0%	0%	< 1%

Serious Respiratory AESIs

Respiratory AESIs	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Bronchospasm serious AESIs	1%	0%	1%
Hemoptysis serious AESIs	3%	5%	3%
COPD exacerbation serious AESIs	3%	2%	3%
Allergic alveolitis serious AESIs	2%	1%	2%

Adverse Events of Special Interest (AESI)

- Respiratory AEs
- Known systemic AE risks with IV amikacin

Known Systemic AEs for IV Amikacin

Amikacin-Related AESI	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Nephrotoxicity	1%	3%	4%
Neuromuscular AEs	2%	0%	3%
Ototoxicity	17%	10%	15%
Tinnitus	8%	1%	7%
Dizziness	6%	3%	6%

Ototoxicity AEs

Amikacin-Related AESI Preferred Terms	Study 212		NTM Pooled
	ALIS + Multidrug Regimen (N=223)	Multidrug Regimen Alone (N=112)	ALIS + Multidrug Regimen (N=388)
Ototoxicity	17%	10%	15%
Tinnitus	8%	1%	7%
Dizziness	6%	3%	6%
Hypoacusis	2%	5%	1%
Balance disorder	1%	0	1%
Deafness	1%	0	1%
Deafness neurosensory	1%	1%	1%
Vertigo	1%	0	1%
Presyncope	< 1%	0	1%

Tinnitus AEs

- 17 of 223 patients reported AE
  - 59% had prior hearing-related history
  - 41% had previous aminoglycoside use
- All mild to moderate
- No AEs led to ALIS discontinuation
- 6 of 17 led to study drug interruption
  - 4 of 6 resolved within 30 days
- Did not resolve in 8 of 17
  - 88% had prior hearing-related history
  - 63% had prior aminoglycoside use

Safety Summary

- Rate of SAEs and AEs leading to death similar between treatment arms
- Respiratory AEs most common with ALIS inhalation therapy
- Majority AEs mild or moderate
- Most AEs resolved without discontinuation of ALIS
- Low risk for IV amikacin-related AEs
- No difference in laboratory shift values

Clinical Perspective

David Griffith, MD

Professor of Medicine

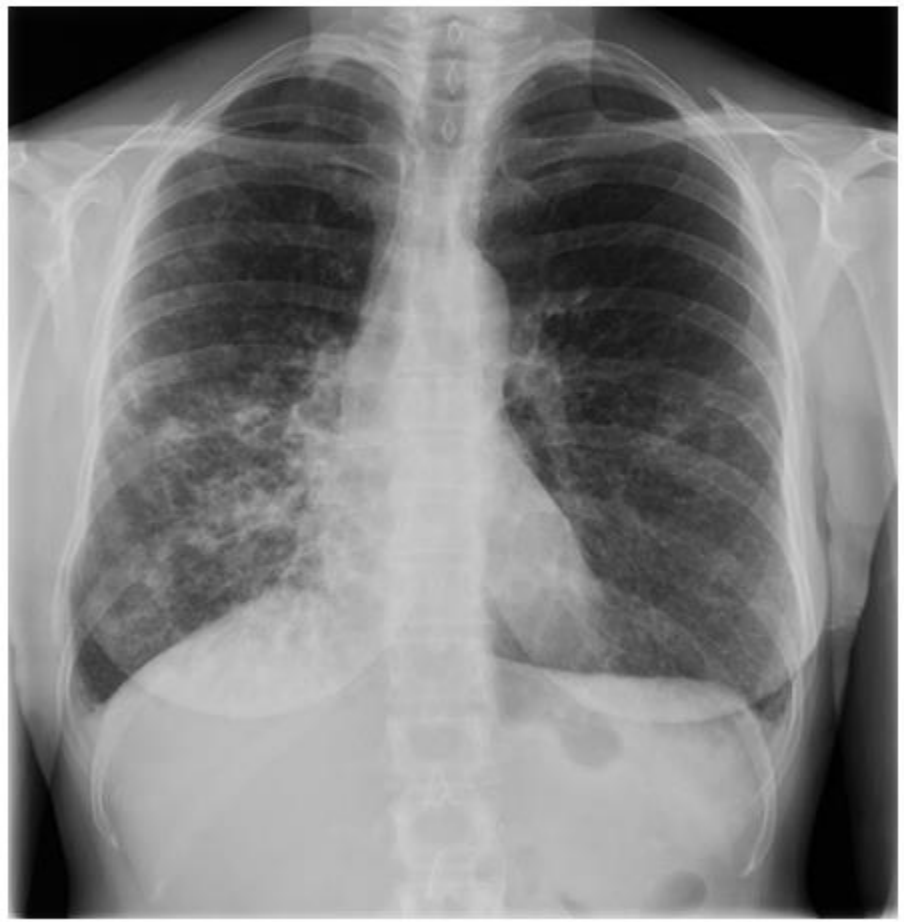
University of Texas Health Science Center at Tyler

NTM Lung Disease Is Debilitating, Potentially Life-Threatening Condition with No Approved Therapy

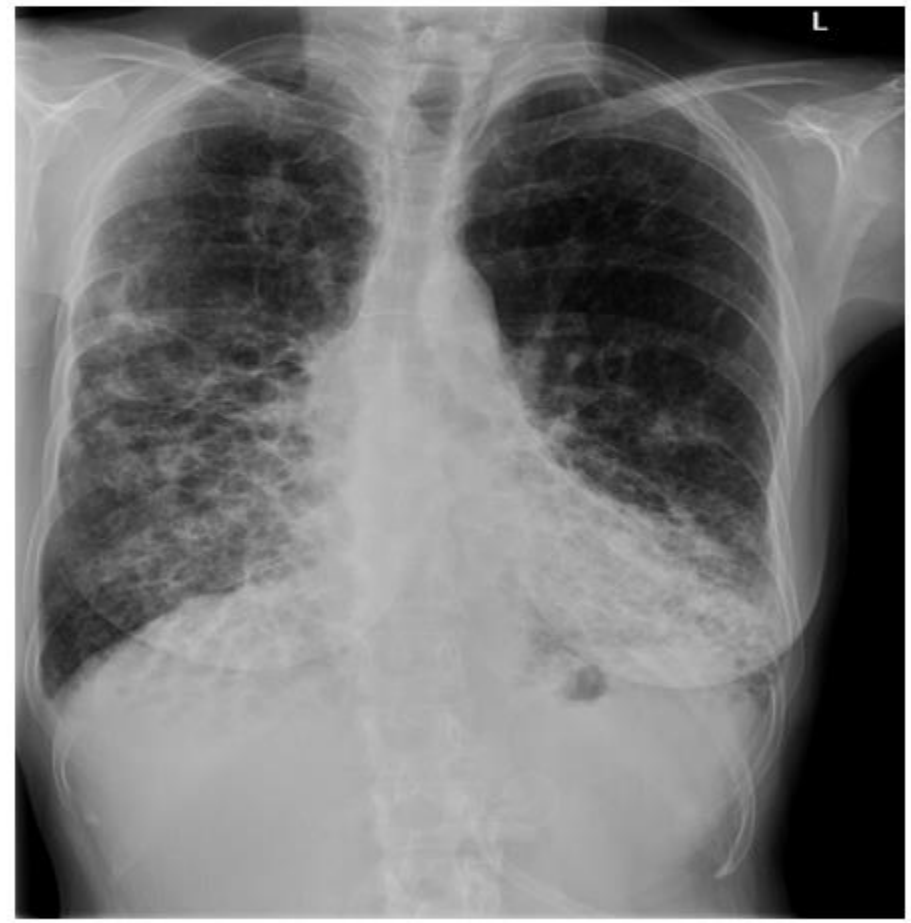
- Goal of treatment is durable eradication of infection
  - Sputum culture negativity
  - Halt disease progression
- Treatment success with macrolide-based regimens not adequate

Radiograph of Patient with Severe MAC Lung Disease

2005



2018



62-year old female with severe bronchiectasis and macrolide resistant MAC

Patients Need More Effective Treatment Options than Available Today

- Current antibiotics not sufficient
- Companion agents have limited potency
- Macrolide is basis of treatment success

ALIS Will Change Treatment Paradigm

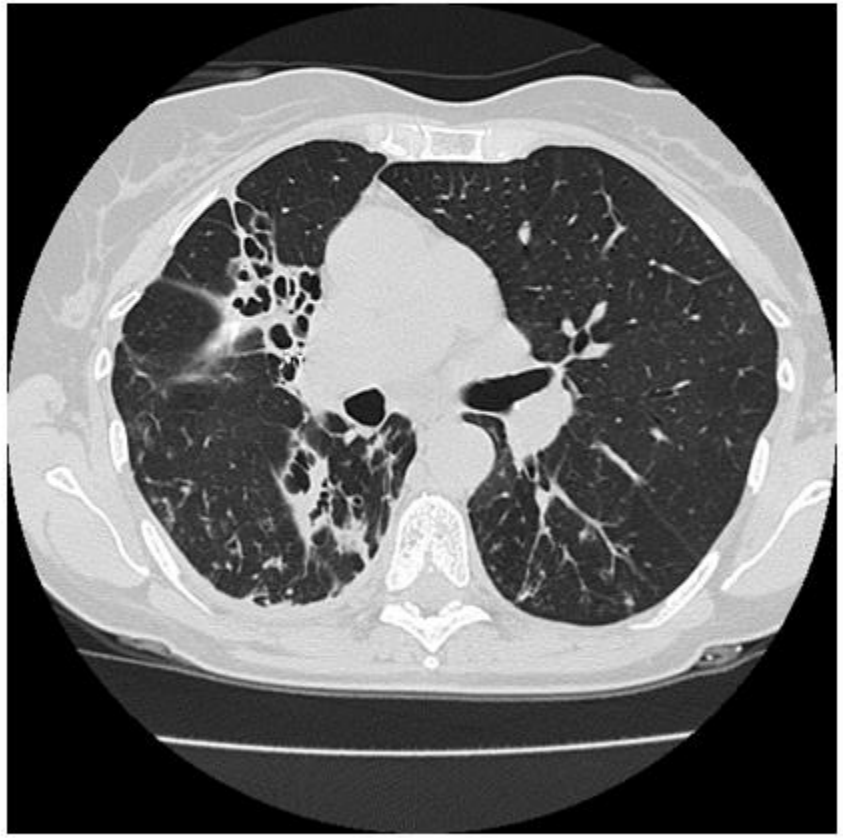
- First advance in > 20 years
- Superior ability to achieve culture conversion
- Conversion among difficult-to-treat patients

ALIS Risks Are Manageable

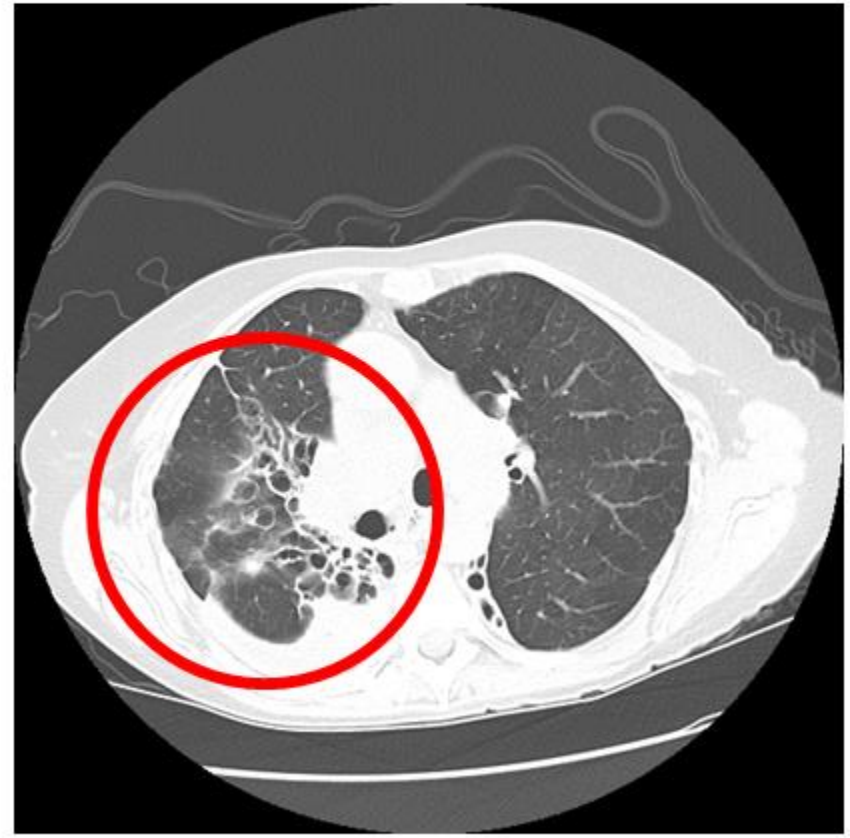
- Respiratory AEs were most commonly reported
- Diligent management of AEs
- Treatment interruptions when needed
- Educating patients and setting expectations

Radiographic Evidence of Extensive Disease Progression in Patient with NTM

2007



2017



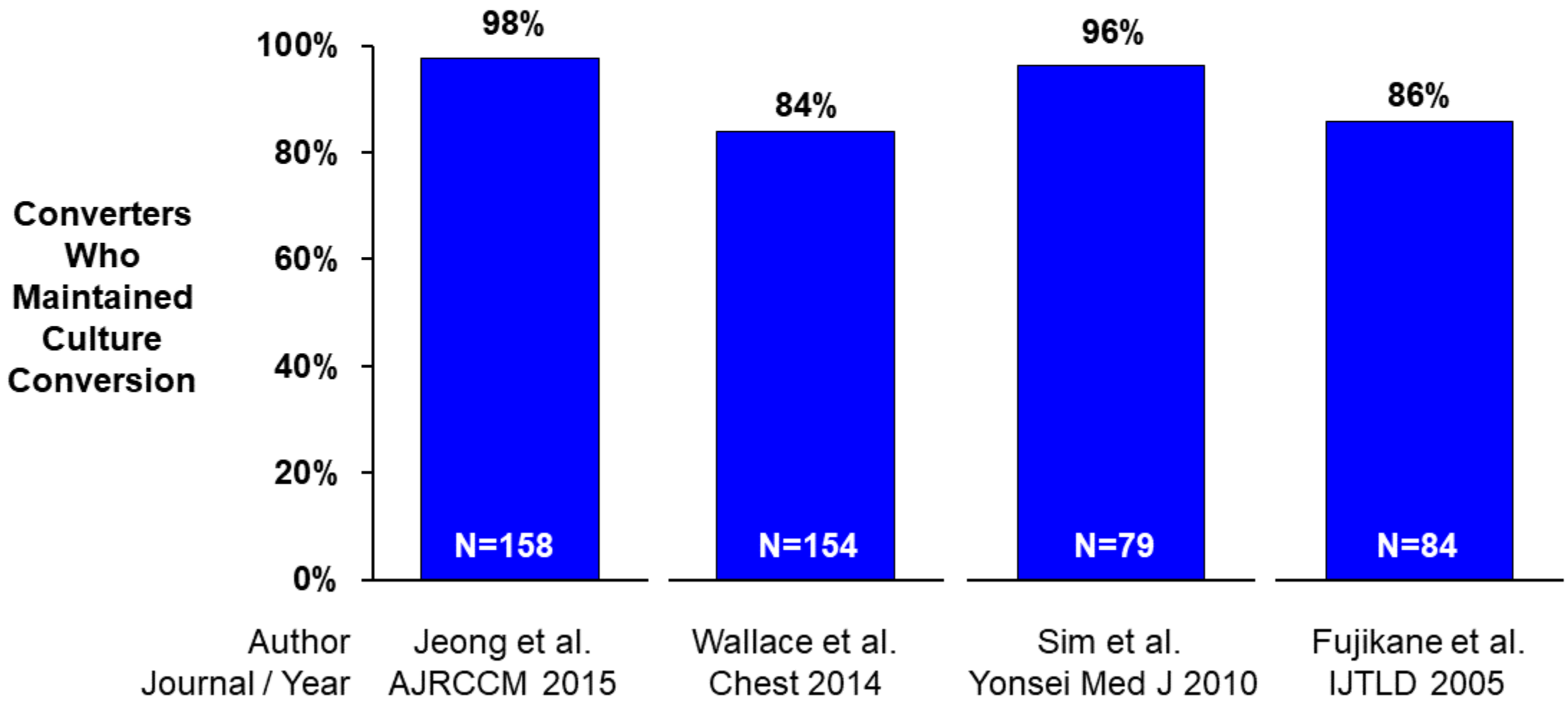
Addition of ALIS to Multidrug Regimen Resulted in First Negative Culture in > 10 Years

- Met Study 112 disease success criteria
  - 12 months negative sputum culture on MAC therapy
- Now off all MAC medications > 6 months
  - Improved symptomatically
  - Improved exercise tolerance and sense of well-being
  - Improved appetite weight gain

Culture Conversion Is First Step Toward Meeting Treatment Success Criteria

- Durable conversion
- Stop all MAC therapy

Culture Conversion Sustained Throughout Course of MAC Therapy



Calculated from manuscript data

Eradication of Organism and Microbiologic Cure Are Beneficial

- Symptomatic benefit
- Functional benefit
  - Spirometry
  - 6MWT
- Reduction in mortality risk

ALIS Benefits Outweigh Risks for Patients With Limited Treatment Options

- Demonstrated superior benefit over standard of care
- ALIS + Multidrug Regimen increases attainment of sputum culture conversion
  - Sustained culture conversion allows patients to stop NTM therapy
- Low systemic exposure
- Acceptable safety profile

ALIS Holds Promise for Other MAC Patients

- ALIS mechanism of action same for new and refractory patients
- Allows patients to get 2 drugs with significant activity demonstrated against MAC
  - Macrolide + amikacin
  - Decreases chance of acquired mutational resistance
- Use supported by extensive experience treating TB
- Chance for early intervention and cure to prevent lung deterioration

Amikacin Liposome Inhalation Suspension (ALIS) for the Treatment of Nontuberculous Mycobacterial (NTM) Lung Disease Caused by *Mycobacterium avium* complex (MAC) in Adults

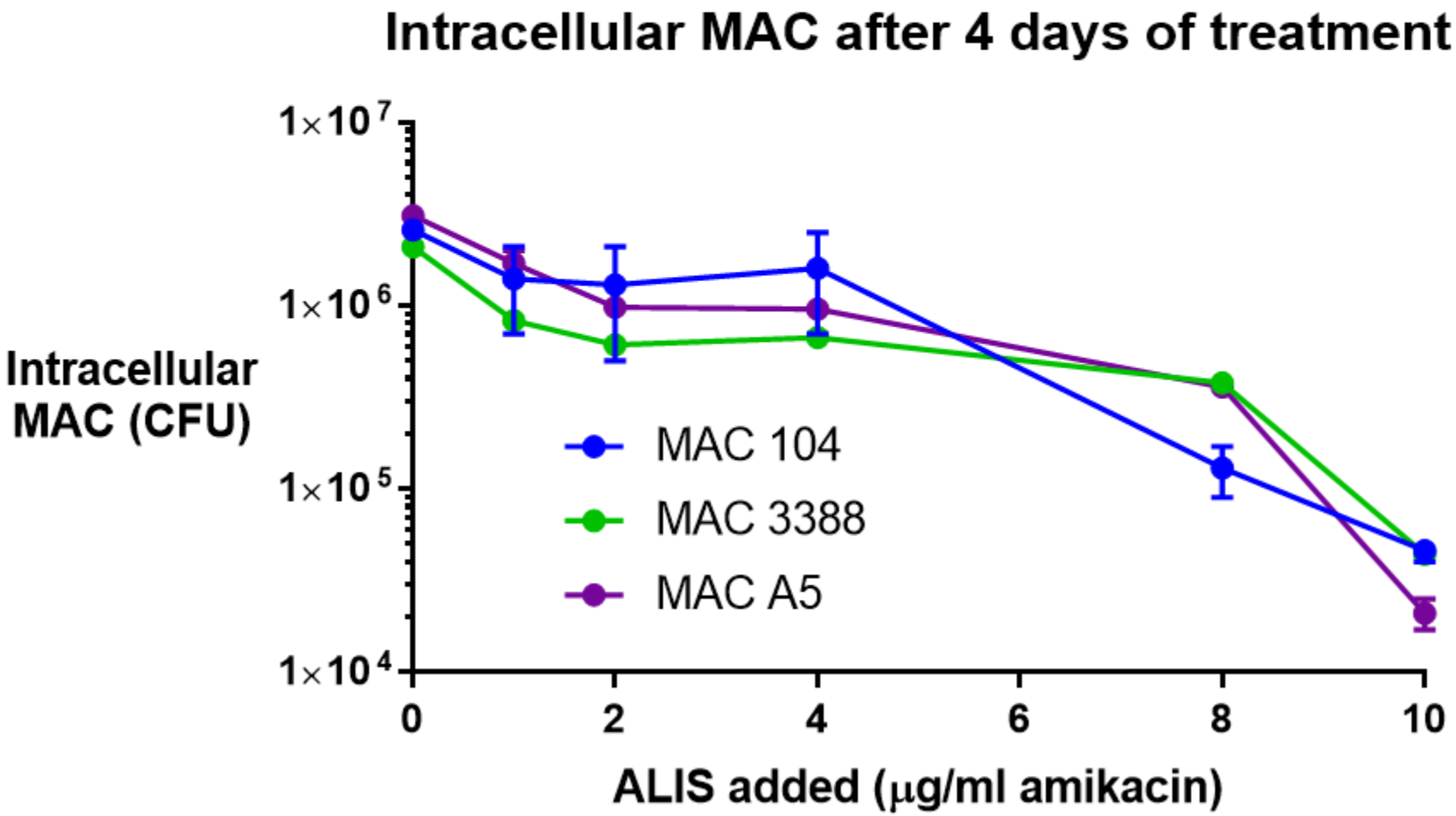
August 7, 2018

Insmed Incorporated

Antimicrobial Drugs Advisory Committee

BACKUP SLIDES

Dose-dependent ALIS Killing of Intracellular MAC



Rose et al, PLOS ONE, 2014

Study 212: Conversion by Baseline Macrolide Susceptibility

All MAC	Clarithromycin Susceptible MIC <32 µg/mL (N=262)	Clarithromycin Resistant MIC ≥32 µg/mL (N=73)
Overall	262	73
Percent Conversion	25.6% (67/262)	10.9% (8/73)
ALIS + Multidrug Regimen	172	51
Percent Conversion	33.7% (58/172)	13.7% (7/51)
Multidrug Regimen Alone	90	22
Percent Conversion	10% (9/90)	4.5% (1/22)

Study 112: Converters

- 20/89 (22.5%) achieved culture conversion by Day 168
- 3 additional converters during 28-day off-treatment period
- 19 non-CF MAC
- 2 non-CF Mab
- 2 CF Mab

Study 212: Combinations of Multidrug Regimen at Baseline

Drug combination	ALIS + Multidrug Regimen Total (N=223)	Multidrug Regimen Alone Total (N=112)
E/M/R/O	30 (14)	8 (7)
E/M/R	123 (55)	61 (55)
E/M/O	6 (3)	6 (5)
E/M	13 (6)	3 (3)
E/R/O	8 (4)	6 (5)
E/R	3 (1)	1 (1)
E/O	1 (0.4)	0
M/R/O	13 (6)	12 (11)
M/R	13 (6)	5 (5)
M/O	9 (4)	6 (5)
R/O	1 (0.4)	1 (1)
O	1 (0.4)	0

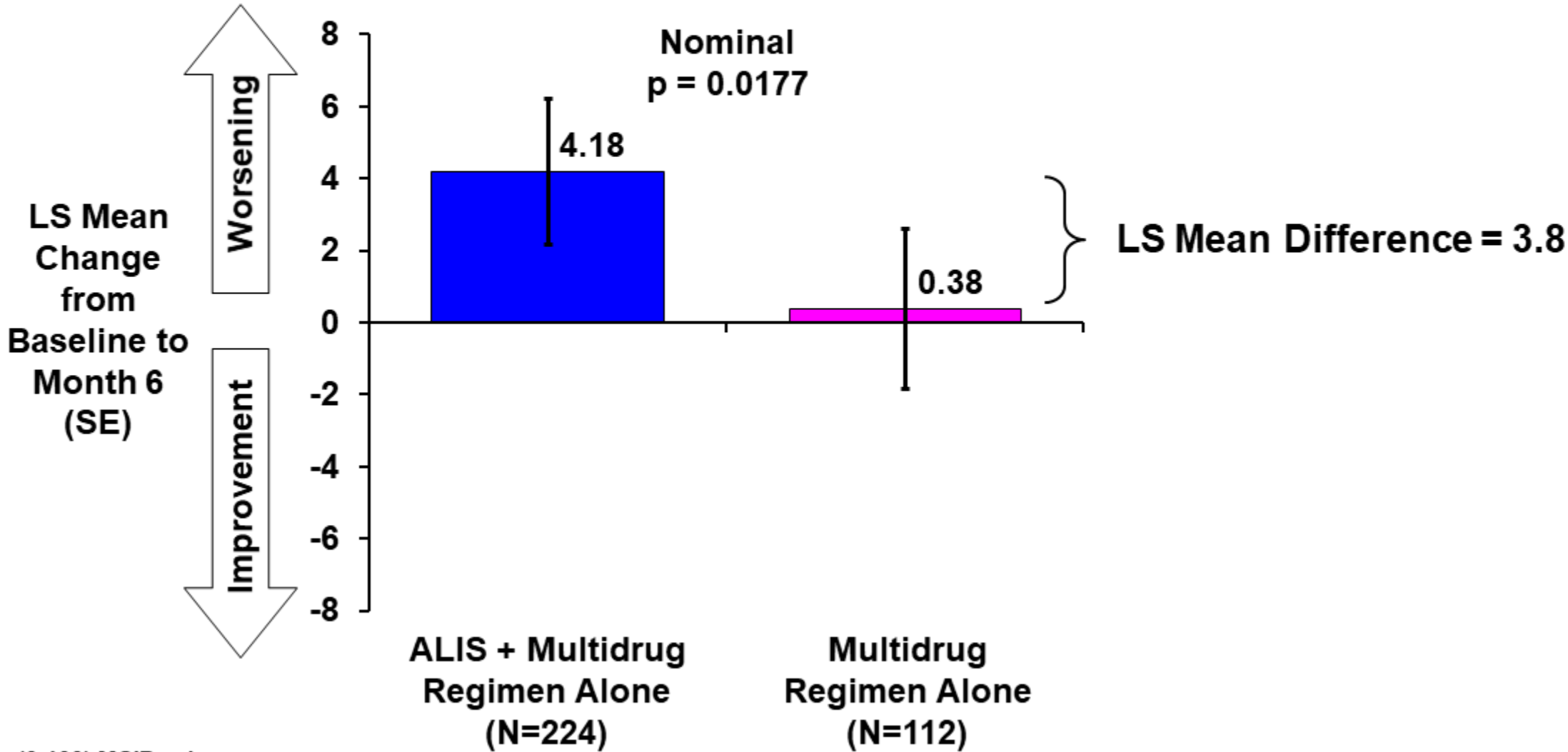
(*): In drug combinations, letter 'E' stands for Ethambutol class, 'M' for Macrolide class, 'R' for Rifamycin class and 'O' for Other MDR class.

Study 212: Culture Conversion Was Uncommon in Patients with Amikacin MIC >64 µg/mL

- ALIS + Multidrug Regimen
  - 1/24 (4.2%) converted with amikacin MIC >64 µg/mL
- Multidrug Regimen Alone
  - no subjects converted with amikacin MIC >64 µg/mL

ALIS + Multidrug Regimen: 1 subject converted, then developed amikacin MIC >64 µg/mL and subsequently reverted to MIC <64 µg/mL

Study 212: Secondary Endpoint SGRQ Total Score Change from Baseline to Month 6



SGRQ Total Score (0-100) MCID = 4

Study 212: Compliance Rate in ALIS + Multidrug Regimen Arm (Baseline to Data Cutoff)

% Compliance	ALIS + Multidrug Regimen (N=223)
> 120%	1 (0.4%)
80% to 120% (inclusive)	149 (66.8%)
< 80%	73 (32.7%)

Study 112: Systemic Bioavailability of ALIS

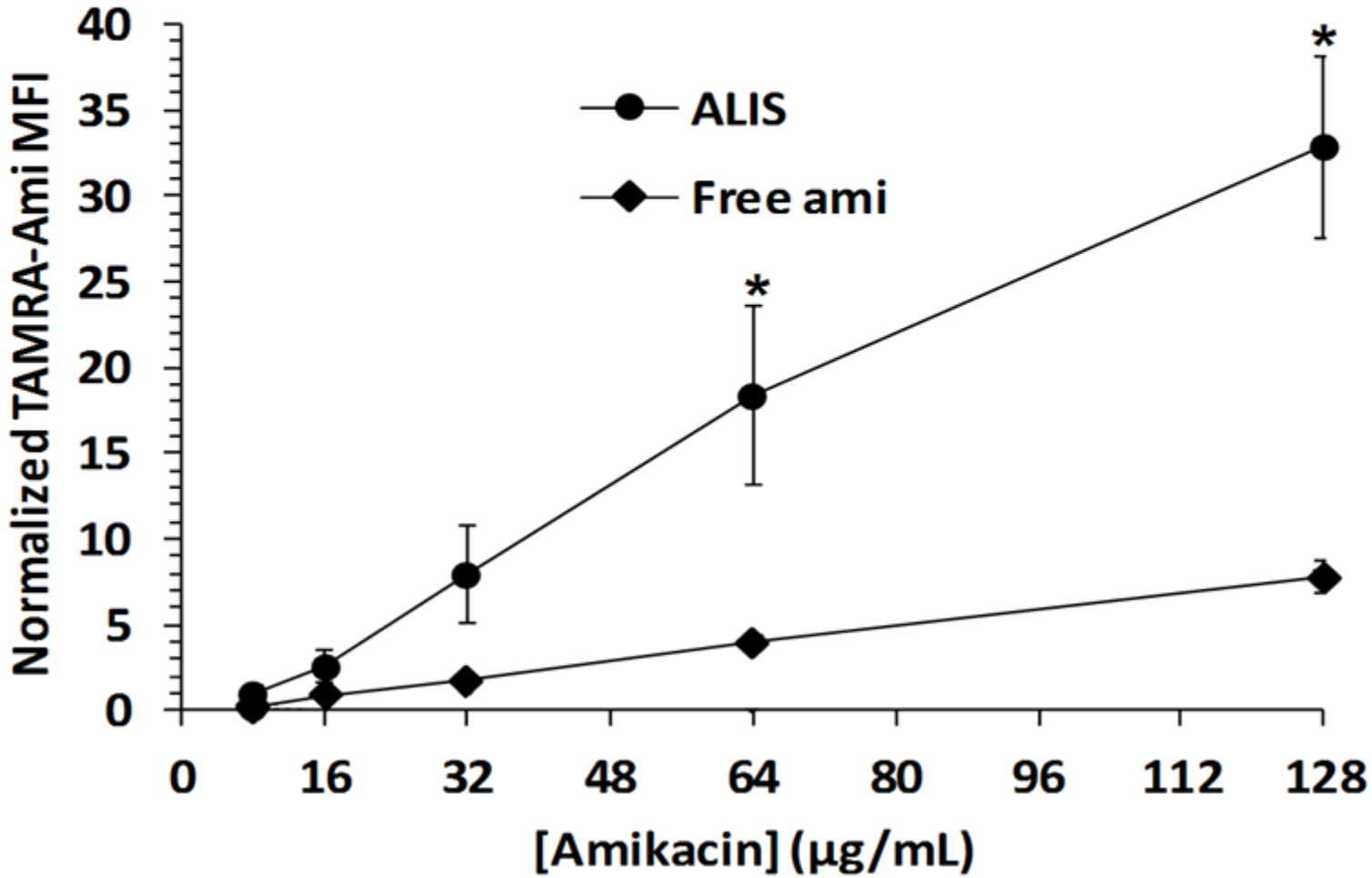
		Percent of Dose Excreted in the Urine Over a Dosing Interval	
Day	N	Mean (% CV)	Median (Range)
Day 1	6	4.46 (54.8)	3.25 (2.71 to 8.95)
Day 84	6	7.74 (77.5)	6.88 (1.55 to 17.2)
Day 168	11	8.85 (70.3)	8.42 (0.72 to 22.6)

Amikacin Serum Exposure Is Lower After ALIS Compared to Systemic Administration

Description	Dose/Route	N	AUC_{24}, Steady State (µg*h/mL)[a]	C_{max}, Steady State (µg/mL)[a]
Phase 2 NTM (TR02-112)	590 mg QD ALIS, Inhaled	14	21.3 (70.0)	2.01 (74.2)
Phase 3 NTM (INS-212)	590 mg QD ALIS, Inhaled	39	20.0 (55.2)	2.32 (59.7)
Phase 3 CF (TR02-108)	560 mg QD ALIS, Inhaled	29	7.81 (4.34)	1.08 (0.720)
MDR-TB Patients[b]	15-25 mg/kg QD, IM	28	~550	~45
CF Patients[c]	30-35 mg/kg QD, IV	12	235 (46.8)	116 (31.9)
Healthy Volunteers[d]	7.5 mg/kg single dose, IV	6	66.6 (23.6)	~35[e]

[a]Summary statistics presented as mean (CV%)
[b]Modongo et al. Antimicrob Agents Chemother 2015;59(10):6337-6343
[c]Byl et al. J Antimicrob Chemother. 2001;48:325-327
[d]Garraffo et al. Antimicrob Agents Chemother. 1990;34:614-621.
[e]Based on review of mean concentration-time profile figure in publication.

ALIS Significantly Improves Amikacin Uptake Into Macrophages Compared With Free Amikacin *In Vitro*



~4 fold increase over free amikacin over the dose range

Zhang *et al*, Frontiers in Microbiology, 2018.

Study 212: Patient with 10 Hospitalizations in the ALIS + Multidrug Arm

- 76-year-old current smoker (50 pack/year)
- Medical History: COPD, bronchiectasis, hearing loss, fibromyalgia, ischemic heart disease, and hypothyroidism
- 3 hospitalizations during screening period
  - Exacerbation of bronchiectasis, lower respiratory tract infection, infective exacerbation of COPD
- 10 hospitalizations during study
  - COPD **X 3**, infective exacerbation of bronchiectasis **X 2**, diarrhea **X 2**, infective exacerbation of COPD **X 2**, abdominal pain, spinal pain
- Remained on ALIS with no interruption